Subject No: [redacted]
Treatment: Parent study and regimen: 20110117; Evolocumab SC QM 420 mg Year 1: Standard of care
Report: Coronary revascularization

Subject [redacted] was a 60-year-old white man participating in Study 20120138 who was diagnosed with multivessel coronary artery disease (reported term: revascularization [multivessel coronary artery disease]). The subject's medical history included hyperlipidemia, heterozygous familial hypercholesterolemia, and family history of ischemic heart disease. The subject was a nonsmoker and had no known cardiac disease, nephropathy, or drug allergies. Previous and ongoing treatment for hyperlipidemia included ezetimibe and rosuvastatin since 17 May three years ago*. No relevant concomitant medications were reported.

The subject received evolocumab in the parent study (Study 20110117) from 13 August same year* to 08 October same year*, and was randomized to standard of care in Study 20120138 on 04 November [redacted].

On 12 December same year*, the subject underwent coronary computed tomography angiogram (CTA) which showed multiple calcified lesions. Significant lesions were seen in the distal right coronary artery and in the postero-lateral branch ostium, with possible significant lesions in the medial anterior descending and the proximal circumflex artery. Four days later on 16 December same year*, CTA showed again multiple lesions in 3 vessels, but the subject never experienced angina on exertion or at rest.

On 14 January one year after*, the subject underwent computerized axial tomography of coronary arteries which detected multivessel coronary artery disease and was hospitalized. The same day, laboratory tests did not reveal any acute abnormality and serial cardiac enzymes were normal: creatine kinase was 1 U/L, and troponin I was 0. Additionally, electrocardiogram showed sinus rhythm of 65 beats per minute with normal axis, normal PR segment, non-widened QRS, no ST imbalances, and normal T waves.

On 16 January one year after*, the subject underwent cardiac catheterization, which showed slightly enlarged left ventricle with normal global systolic function with ejection fraction 68% and left ventricular end diastolic pressure of 9 mmHg. The same day, the subject underwent percutaneous transluminal coronary angioplasty with placement of 6 stents, 2 of which were drug eluting. Treatment medications after the onset of event included prasugrel,

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acetylsalicylic acid, eplerenone, omeprazole, ramipril, bisoprolol, rosuvastatin, and ezetimibe. The outcome of event multivessel coronary artery disease was reported as resolved on 19 January one year after* and the subject was discharged from hospital on the same day. The subject was advised to follow up with the cardiology department within 6 months.

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

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

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Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110117, Evolocumab SC Q2W 140 mg Year 1: Evolocumab SC QM 420 mg + Standard of Care
Report: Nephrolithiasis

Subject [redacted] was a 48-year-old white man participating in Study 20120138 who developed nephrolithiasis (reported term: kidney stones). The subject's medical history included primary hyperlipidemia, mixed dyslipidemia, left-sided kidney stones, and atherosclerosis. Concomitant medications included acetylsalicylic acid. Previous and ongoing treatment for primary hyperlipidemia and mixed dyslipidemia included atorvastatin.

The subject received evolocumab in the parent study (Study 20110117) from 08 April same year* to 17 June same year*. He received the first dose of evolocumab in Study 20120138 on 23 July [redacted]. Approximately 5 months later, on 17 September same year*, the subject had a sudden onset of pain due to nephrolithiasis, which he recognized since he had had several attacks of left-sided kidney stones in the past. The subject was presented in the emergency room, where he received treatment with diclofenac, tamsulosin, ofloxacin, and a combination of acetylsalicylic acid, caffeine, orphenadrine, and phenacetin. On 19 September same year*, the pain subsided. Then, on 20 September same year*, the subject experienced a new onset of pain accompanied by blood in the urine; therefore, he was admitted to the hospital for observation. A catheter was inserted and bladder was flushed continuously from 20 September same year* until 21 September same year*, when the hematuria stopped. Additionally, the subject received intravenous diclofenac. The event of nephrolithiasis was reported as resolved on 22 September same year* and the subject was discharged from the hospital. No laboratory data were available. The subject continued in the study.

The date of the subject's last dose of evolocumab prior to the event was on 20 August same year*. Evolocumab was continued. The subject was continuing home dosing as of the data cutoff date of [redacted] and the last in-clinic dose was documented on 02 January one year after*.

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

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Subject No: [redacted]
Treatments: Parent study and regimen: Study 20120348, Evolocumab SC Q2W 140 mg Year 1: Evolocumab SC Q2W 140 mg + Standard of Care
Report: Osteoarthritis

Subject [redacted] was a 65-year-old white man participating in Study 20120138 who developed osteoarthritis (reported term: worsening of osteoarthritis of right knee). The subject's medical history included gout, osteoarthritis of left knee in eleven years ago*, right knee pain since six years ago*, left total knee replacement in March three years ago*, osteoarthritis of left wrist in 2010, hypercholesterolemia since January one year ago*, and osteoarthritis of right knee since 31 May same year*. Previous treatment for hypercholesterolemia included rosuvastatin. Other concomitant medications included levothyroxine, lansoprazole, celecoxib and ubidecarenone.

The subject received evolocumab in the parent study (Study 20120348) from 02 May same year* to 30 May same year*. The subject received the first dose of evolocumab in Study 20120138 on 09 July [redacted].

On 02 December same year*, the subject experienced worsening of osteoarthritis of the right knee and was hospitalized for a total right knee replacement. Treatment included enoxaparin, ferrous sulfate, oxycodone and paracetamol. Additional treatment after the onset of event included physiotherapy from 03 December same year* to 03 January one year after*. The event of worsening of osteoarthritis of the right knee was reported as resolved on 05 December same year* and the subject was discharged from the hospital on the same day.

The subject's last dose of evolocumab prior to the event was on 26 November same year*. As of the data cutoff date of [redacted], home dosing was continuing and the last in-clinic dose was documented on 01 October same year*.

The investigator reported that there was not a reasonable possibility that the event worsening of osteoarthritis of right knee was related to investigational study drug.

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Subject No: [redacted]
Treatment: Parent study and regime: Study 20120348, Evolocumab SC Q2W 140 mg Year 1: Standard of Care
Report: Umbilical hernia

Subject [redacted] was a 48-year-old white man participating in Study 20120138 who developed an umbilical hernia. The subject's medical history included primary hyperlipidemia, mixed dyslipidemia, hypercholesterolemia, umbilical hernia, obesity, and exercise-induced asthma. Concomitant medications included salbutamol and mometasone. Previous and current treatment for primary hyperlipidemia or mixed dyslipidemia included rosuvastatin.

The subject received evolocumab in the parent study (Study 20120348) from 02 May same year* to 31 May same year*, and was randomized to the standard of care arm in Study 20120138 on 02 July [redacted].

The subject had an umbilical hernia since 07 March two years ago*. On 24 August same year* the subject began lifting weights. Subsequently, the subject experienced a sudden onset of abdominal pain near the umbilical hernia area. An abdominal computerized tomography revealed an umbilical hernia. Approximately 1 month and 3 weeks after randomization to Study 20120138, on 26 August same year*, the subject was hospitalized and underwent an umbilical hernia repair. Treatment for post-surgical pain management included paracetamol, Atasol compound (acetaminophen, caffeine, codeine), and ibuprofen. The event of umbilical hernia was reported as resolved on 29 August same year*, and the subject was discharged from the hospital on that day.

The investigator reported that there was not a reasonable possibility that the event of umbilical hernia was related to the study conduct.

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

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Subject No: [redacted]
Treatments: Parent study and regimen: Study 20120348, Evolocumab SC Q2W 140 mg Year 1: Evolocumab SC Q2W 140 mg + Standard of Care
Report: Myocardial infarction, Coronary artery stenosis

Subject [redacted] was a 66-year-old white man participating in Study 20120138 who experienced coronary artery stenosis and myocardial infarction (reported term: mid left anterior descending stenosis). The subject's medical history included primary hyperlipidemia since 18 February ten years ago*, mixed dyslipidemia, and type 2 diabetes. The subject did not have a medical history of smoking or hypertension. Concomitant medications included acetylsalicylic acid, metformin, pantoprazole, and bivalirudin. Previous treatment for the primary hyperlipidemia and mixed dyslipidemia included rosuvastatin.

The subject received evolocumab in the parent study (Study 20120348) from 07 May same year* to 04 June same year*. The subject received the first dose of evolocumab in Study 20120138 on 26 July [redacted].

On 28 November same year*, the subject was seen in the emergency room due to intermittent chest pain. Physical examination showed a body temperature of 36.3°C, pulse rate of 63 beats per minute (bpm), respiratory rate of 20 breaths per minute, oxygen saturation of 98% and blood pressure (BP) of 139/85mmHg. Chest radiograph was unremarkable. An electrocardiogram (ECG) revealed recent myocardial infarction with inferior T-wave changes and elevated troponin level of 3.60 ng/mL. There were no other acute significant laboratory abnormalities. The subject was admitted to the hospital on the same day.

On 29 November same year*, an echocardiogram revealed segmental wall motion abnormality with normal left ventricular size and overall global systolic function, hypokinesia of the basal and mid segment of the inferolateral wall and no obvious significant valvular abnormalities. Heart rate was 50 per minute, BP was 107/62 mmHg.

On 01 December same year*, ECG revealed a ventricular rate of 48 bpm, PR interval of 196 ms, QRS of 78 ms, QT/QTc of 442/394 ms, P-R-T axes of 44 0 -75, and T-wave abnormality, consistent with inferolateral ischemia.

On 02 December same year*, the subject underwent coronary angiography, which revealed 95% ruptured plaque in mid circumflex and mid left anterior descending (LAD) stenosis of 80% in a small calibre vessel. Successful percutaneous coronary intervention was performed in the circumflex artery using a drug-eluting stent.

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Treatment after the onset of the event included atorvastatin, acetylsalicylic acid, perindopril, metoprolol and ticagrelor. Other concomitant medication included pantoprazole and simvastatin. The ongoing concomitant medication also included metformin which was given to the subject after the event was resolved.

On 03 December same year*, the event was considered as resolved, and the subject was discharged from the hospital in a good condition. Evolocumab was withheld as the subject was scheduled for angioplasty for a second stent insertion on 06 January one year after*. The last dose of investigational product prior to the event was on 22 November same year*.

On 06 January one year after*, subject was hospitalized and underwent scheduled coronary angioplasty with drug eluting stent for mid LAD stenosis. The previous stent in the circumflex artery was noted to be patent. The investigator reported that this was not emergency procedure. On the same day, physical examination showed blood pressure of 100/60 mmHg with a heart rate of 45 bpm and ECG showed T wave abnormality and inferior ischemia. The outcome of event LAD stenosis was reported as resolved on 07 January one year after* and the subject was discharged from hospital on the same day.

Since discharge, the subject was feeling well, and had returned back to his usual exercise activities including swimming without any problems or shortness of breath or chest discomfort. The investigator reported that the subject should be continued on dual antiplatelet therapy for 1 year, at which point the ticagrelor could be stopped.

The subject's last dose of evolocumab prior to event was on 22 November same year*. As of the data cutoff of [redacted], home dosing was continuing with the last in-clinic dose documented on 12 June one year after*.

The investigator reported that there was not a reasonable possibility that the event of non ST elevation MI was related to evolocumab or to device.

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Subject No: [redacted]
Treatments: Parent study and regimen: Study 20120348; Evolocumab SC Q2W 140 mg Year 1: Evolocumab SC QM 420 mg + Standard of care
Report: Bladder neoplasm, Ureteric calculus

Subject [redacted] was a 76-year-old white man participating in Study 20120138 who developed a bladder neoplasm (reported term: bladder tumor) and a ureteral calculus (reported term: left ureteral stone). The subject's medical history included dyslipidemia, previous smoking, COPD, macular degeneration, obesity, benign prostatic hyperplasia (BPH), and previoustransurethral resection of the prostate (TURP), with persistent irritative symptoms. Concomitant medications included glyceryl trinitrate, clopidogrel, diltiazem, trazodone, ipratropium bromide, pantoprazole, tiotropium, budesonide with formoterol, theophylline, cholecalciferol, losartan, and metoprolol. Previous and ongoing treatment for dyslipidemia included atorvastatin.

The subject received evolocumab in the parent study from 01 August same year* to 29 August same year*. The subject received the first dose of evolocumab in Study 20120138 on 15 October [redacted].

On 20 January one year after*, urinalysis showed clinically significant microscopic hematuria and low volume pyuria. On the same day, the subject underwent cystoscopy which revealed chronic changes in bladder mucosa consistent with long-standing benign prostatic hyperplasia and a small, 5 to 7 mm papillary tumor. A large left proximal ureteral stone was also identified.

On 27 January one year after*, computed tomography (CT) scan confirmed a left ureteral stone of 10 x 13 mm in size and bladder tumor, and also revealed a smaller left renal stone. Subsequently on 04 February one year after*, the subject was hospitalized and underwent cystoscopy for transurethral resection of 2 small bladder tumors. The subject had a large left proximal ureteral stone as well as a small papillary bladder tumor. The tumor was estimated to be 1 cm in size. The subject also underwent left retrograde pyelogram and left ureteral stent placement. Procedures were without complications. Preoperative and postoperative diagnosis included left proximal ureteral stone and bladder tumor consistent with transitional cell carcinoma. The investigator confirmed that the subject did not have any etiological or pre-disposing risk factors associated with the event and also none of the concomitant medications were suspect. The outcome of the event bladder tumor was reported as resolved on 05 February one year after* and the subject was discharged from the hospital on the same day.

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On 07 March one year after*, the subject underwent a planned extracorporeal shock wave lithotripsy (ESWL) for the left ureteral stone, which showed modest changes and some distal migration.

On 28 March one year after*, the subject underwent left ureteroscopy and holmium laser lithotripsy, and the stone fragments were removed without difficulty. On the same day, the subject underwent a successful left ureteral stent placement. The subject was hospitalized and discharged on the same day. The outcome of the event of left ureteral stone was reported as resolved on 28 March one year after*. Two days later on 31 March one year after*, the left ureteral stent was removed without any complications. Treatment after the onset of event included fentanyl, lidocaine, propofol, midazolam, hydrocodone with paracetamol, ondansetron, and rocuronium.

The subject's last dose of evolocumab before the events was on 07 January one year after*. The subject was continuing home dosing as of the data cutoff date of [redacted] and the last in-clinic dose was documented on 07 January one year after*.

The investigator reported that there was not a reasonable possibility that the events of bladder tumor and left ureteral stone were related to evolocumab or to the device.

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Subject No: [redacted]
Treatments: Parent study and regimen: Study 20120348, Evolocumab SC Q2W 140 MG AI Year 1: Evolocumab SC Q2W 140 mg + Standard of Care
Report: Ventricular tachycardia

Subject [redacted] was a 69-year-old white man participating in Study 20120138 who experienced ventricular tachycardia (reported term: intermittent ventricular tachycardia). The subject's medical history included dyslipidemia, ventricular tachycardia, automatic implantable cardioverter defibrillator insertion, hypercholesterolemia, hypertension, diabetes mellitus, coronary artery disease, coronary artery bypass, myocardial infarction, congestive heart failure, cardiac arrest, dyspnea, neuropathy, renal insufficiency, and sleep apnea. Concomitant medications included carvedilol, ramipril, acetylsalicyclic acid, omeprazole, sitagliptin, glibenclamide, insulin, meclizine, and torsemide. Previous treatment for dyslipidemia included ezitimibe and simvastatin (stopped on 17 March one year after*). Ongoing treatment for dyslipidemia included fish oil, atorvastatin, and simvastatin.

The subject received evolocumab in the parent study from 03 May same year* to 31 May same year*. The subject received the first dose of evolocumab in Study 20120138 on 28 June [redacted].

On 07 March one year after*, the subject had insertion of an automatic implantable cardioverter defibrillator (AICD). On 18 March one year after*, the subject felt dizzy, the AICD fired again, and the subject developed intermittent ventricular tachycardia. The subject was hospitalized on the same day for further evaluation. On 19 March one year after*, a cardiac catheterization was done which was negative. On the same day, the subject's laboratory tests revealed creatine phosphokinase level to be 44 U/L and creatine phosphokinase MB 1.4 ng/mL. The subject's cardiac enzymes were noted to be negative. On 20 March one year after*, the subject was discharged from the hospital and the outcome of the event intermittent ventricular tachycardia was reported as resolved on that date. Treatment medication after the onset of event included sotalol, hydromorphone, midazolam, and ondansetron.

The subject's last dose of evolocumab prior to the event was on 06 March one year after*. As of the data cut-off date of [redacted], evolocumab home dosing was continued and the last in-clinic dose was documented on 06 March one year after*, the subject continued in the study.

The investigator reported that there was not a reasonable possibility that the event of intermittent ventricular tachycardia was related to investigational study drug or to the auto-injector device.

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Subject No: [redacted]
Treatments: Parent study and regimen: Study 20120348, Evolocumab SC Q2W 140 MG PFS Year 1: Evolocumab SC QM 420 mg + Standard of Care
Report: Chest pain

Subject [redacted] was a 70-year-old white man participating in Study 20120138 who experienced chest pain (reported term: exertional chest pain). The subject's medical history included dyslipidemia, hyperlipidemia, hypertension, paroxysmal atrial fibrillation, coronary artery disease, percutaneous coronary intervention, myocardial infarction, benign prostatic hyperplasia, and insomnia. Concomitant medications included metoprolol, dronedarone, diltiazem, finasteride, trazodone, zolpidem, paroxetine, silodosin, lisinopril and dabigatran. Treatment for dyslipidemia and hyperlipidemia included atorvastatin.

The subject received evolocumab in the parent study from 12 June same year* to 10 July same year*. The subject received the first dose of evolocumab in Study 20120138 on 07 August [redacted].

On 30 December same year*, the subject experienced exertional chest pain, following several days of epigastric discomfort. The subject presented to emergency room and was placed on telemetry. Two days later, on 01 January one year after*, the subject was hospitalized. On the same day, the subject underwent laboratory tests, which revealed blood levels of creatine phosphokinase (CPK) 211 to 236 U/L, blood creatine kinase (CK) MB 1.6 to 2.0 ng/mL, and troponin I < 0.01 ng/mL. On 02 January one year after*, the subject again underwent laboratory tests, which revealed CPK 198 U/L, CK MB 1.2 ng/mL, and troponin I < 0.01 ng/mL. On 03 January one year after*, the subject underwent left heart catheterization with percutaneous transluminal coronary angioplasty, and a stent to first diagonal was placed for in-stent restenosis. The following day, 04 January one year after*, CPK was 148 U/L and CK MB was 3.8 ng/mL. Treatment medication after the onset of the event included clopidogrel, losartan, glyceryl trinitrate, pantoprazole, and diazepam. The outcome of the event exertional chest pain was reported as resolved on 04 January one year after*, and the subject was discharged from the hospital on the same day.

The subject's last dose of evolocumab prior to the event was on 26 December same year*, which was also the last in-clinic dose documented. As of the data cutoff date of [redacted], evolocumab home dosing was continuing and the subject continued in the study.

The investigator reported that there was not a reasonable possibility that the event of exertional chest pain was related to evolocumab or to the device.

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Subject No: [redacted]
Treatment: Parent Study and regime: Study 20120348, Evolocumab SC Q2W 140 mg Year 1: Evolocumab SC Q4W 140 mg + Standard of care
Report: Cholelithiasis, Postoperative abscess

Subject [redacted] was a 74-year-old white man participating in Study 20120138 who developed cholelithiasis (reported term: cholelithiasis) and abscess (reported term: abscess, postoperative). The subject's medical history included hyperlipidemia, angina due to atherosclerotic coronary disease, coronary artery disease, hypertension, myocardial infarction, percutaneous coronary intervention, tricuspid valve incompetence, chronic obstructive pulmonary disease, benign prostatic hyperplasia with transurethral prostatectomy, polyarthritis, gastroesophageal reflux disease, proteinuria, and psoriasis. Concomitant medications included acetylsalicylic acid, metoprolol, lisinopril, omeprazole, and fluticasone. Previous and ongoing treatment for hyperlipidemia or mixed dyslipidemia included simvastatin.

The subject received evolocumab in the parent study (Study 20120348) from 19 June same year* to 17 July same year*, and received the first dose of evolocumab in Study 20120138 on 16 August [redacted].

On 20 October same year*, the subject experienced right upper quadrant pain, nausea, and vomiting with chills and fever. On 22 October same year*, the subject was diagnosed cholelithiasis and was hospitalized. Simvastatin was withheld on 22 October same year*, while acetylsalicylic acid, lisinopril, and omeprazole were withheld on 23 October same year*.

On 23 October same year*, laboratory tests revealed total bilirubin of 1.7 mg/dL, alkaline phosphatase of 200 U/L, alanine aminotransferase (ALT) of 205 U/L, aspartate aminotransferase (AST) of 75 U/L, albumin of 2.6 g/dL, total protein of 5.5 g/dL, and creatinine of 1.1 mg/dL. Abdominal computerized tomography showed diverticulosis without evidence of diverticulitis, and sludge, puss, and small gravel in the gallbladder. On an unknown date in October same year*, endoscopic retrograde cholangiopancreatography and endoscopic ultrasound were performed. The subject underwent biliary stenting, common bile duct stone extraction, and sphincterectomy. On 25 October same year*, subject underwent uncomplicated laparoscopic cholecystectomy and intraoperative cholangiogram. The postoperative diagnosis was given as chronic cholecystitis and common bile duct stone. On 26 October same year*, repeat laboratory tests revealed alkaline phosphatase of 143 U/L, ALT of 96 U/L, AST of 47 U/L, albumin of 2.4 g/dL, total protein of

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5.2 g/dL, and creatinine of 0.9 mg/dL. Treatment medications after onset of the event included ceftriaxone, metronidazole, ciprofloxacin, fentanyl, hydromorphone, pantoprazole, famotidine, ondansetron, heparin, fondaparinux, labetalol, midazolam, insulin, benzocaine with menthol lozenges, and propofol.

The event of cholelithiasis was reported as resolved on 27 October same year* and the subject was discharged home on the same day.

The subject's the last dose of evolocumab prior to the event was on 10 October 2013. Evolocumab was continued and the subject continued in the study.

On 02 November same year*, the subject was readmitted to the hospital with severe abdominal pain post laparoscopic cholecystectomy. On admission, a computerized tomogram (CT) scan showed an abscess measuring 5.8 x 6.8 cm in the gallbladder fossa adjacent to the cholecystectomy clips. After drainage, culture test showed *Enterococcus faecalis*. On 03 November same year*, laboratory tests disclosed white blood cell (WBC) count of 12.4 k/mm^3 and on 06 November same year* WBC count of 7.7 k/mm^3. Repeat CT scan of the abdomen showed resolution of the abscess. Treatment for the event included vancomycin, piperacillin, cefalexin, sultamicillin, amoxicillin, clarithromycin and metronidazole. The event abscess was reported as resolved on 08 November same year* and the subject was discharged from the hospital on the same day.

The subject's last dose of investigational product prior to the event was on 30 October same year*. The subject was continuing home dosing as of the data cutoff date of [redacted], and the last in-clinic dose was documented on 17 January one year after*.

The investigator reported that there was not a reasonable possibility that the events of cholelithiasis and postoperative abscess were related to evolocumab or to the device.

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[redacted]

Treatment: Parent study and regimen: Study 20110114, Evolocumab SC QM 420 mg + Placebo PO QD
Year 1: Standard of Care
Report: Diverticulitis
Subject [redacted] was a 47-year-old black woman participating in Study 20120138 who developed diverticulitis (reported term: worsened acute sigmoid diverticulitis). The subject's medical history included hyperlipidemia, mixed dyslipidemia, anaphylactic shock, headache, alcohol use, osteoarthritis, overweight, seasonal allergy, paresthesia, urinary tract infection, and diverticulosis with diverticular bleeding. Concomitant medications included acetylsalicylic acid. Previous and ongoing treatment for primary hyperlipidemia or mixed dyslipidemia included atorvastatin.
The subject received evolocumab and placebo in the parent study (Study 20110114) from 20 February same year* to 15 May same year*. The subject was randomized to the standard of care arm in Study 20120138 on 04 June [redacted].
Approximately 4 months later, on 06 October same year*, the subject experienced a serious adverse event of diverticulitis. The subject presented with bleeding and anemia and severe abdominal pain, and was hospitalized. On 06 October same year*, subject underwent abdominal computed tomography which showed diverticulitis in the region of the transverse colon. On 09 October same year*, ultrasound of right upper quadrant abdomen showed gallstones. Treatment included ciprofloxacin, metronidazole, pantoprazole sodium sesquihydrate, ondansetron, hydromorphone, zolpidem, ferrous sulfate, a combination of hydrocodone bitartrate and paracetamol, iron dextran, and diphenhydramine. On 11 October same year*, the subject was discharged from the hospital. The event of diverticulitis was reported as resolved on 11 November same year*.
As of the data cutoff date of [redacted], the subject was continuing in the study and continuing to receive standard of care treatment.
The investigator reported that there was not a reasonable possibility that the event of diverticulitis was related to study activity or procedure.

[redacted]

Treatment: Parent study and regimen: Study 20110114, Placebo SC QM + Ezetimibe PO QD 10 mg
Year 1: Standard of Care
Report: Urinary tract infection (2 episodes)
Subject [redacted] was a 66-year-old white man participating in Study 20120138 who had 2 episodes of urinary tract infection. The subject's medical history included hyperlipidemia, mixed dyslipidemia, benign prostatic hyperplasia, dyspepsia, and Basedow's disease. Concomitant medications included morniflumate. Previous treatment for hyperlipidemia and dyslipidemia was not provided.
The subject received placebo and ezetimibe in the parent study (Study 20110114) from 07 March same year* to 30 May same year*. The subject was randomized to the standard of care arm in Study 20120138 on 06 June [redacted]. On 15 August same year*, the subject had an elective laser surgery for benign prostatic hypertrophy. On 18 August same year*, the subject developed a serious adverse event of urinary tract infection and was hospitalized. The subject was catheterized. He was discharged from the hospital on 19 August same year*. The event urinary tract infection was reported as resolved on 25 August same year*.
On 29 August same year*, the subject again developed urinary tract infection with urinary retention and was catheterized on the same day until 09 September same year*. The event was reported

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as resolved on 09 September same year*. Treatment included ciprofloxacin, oxybutynin, prednisone, phenazopyridine, finasteride, and nitrofurantoin.
As of the data cutoff date of [redacted], the subject was continuing in the study.
The investigator reported that there was not a reasonable possibility that both the events of urinary tract infection were related to any study activity.

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Subject No: [redacted]
Treatments: Parent study: Study 20120122, Placebo SC QM + Atorvastatin QD 5 mg Year 1 treatment: Standard Of Care
Report: Hepatic function abnormal; Artery dissection

Subject [redacted] was a 52-year-old Asian man participating in Study 20120138 who developed a hepatic function abnormal (reported term: hepatic dysfunction disorder) and artery dissection (reported term: coeliac artery dissection).

The subject's medical history included hypertension, type 2 diabetes mellitus, hyperuricemia, and dyslipidemia. Concomitant medications included amlodipine valsartan, insulin, and febuxostat. Previous or ongoing treatments for dyslipidemia were rosuvastatin and atorvastatin.

The subject received placebo in the parent study from 26 December one year ago* to 21 February same year* and was randomized to standard of care in Study 20120138 on 11 April [redacted].

Approximately 2 months after randomization to standard of care in Study 20120138, on 16 June same year*, the subject developed fever, which continued through 19 June same year*. Treatment included fluid infusion and isepamicin sulfate injection. On 20 March same year*, laboratory test results showed elevated alanine aminotransferase (ALT) and normal for aspartate aminotransferase (AST) and blood lactate dehydrogenase (LDH) (see below table). On 19 June same year*, laboratory test results were elevated for AST, ALT, and LDH. On 20 June same year*, the subject's physician suspected liver dysfunction, and on 23 June same year*, the subject was hospitalized for further investigation of hepatic function disorder. AST, ALT, and LDH remained elevated on 23 June same year*, and on 10 July same year*, ALT remained elevated while AST and LDH had returned to normal. On 07 August same year*, laboratory results were normal for ALT and AST and unavailable for LDH. The investigator reported that the reason for hepatic function abnormal was still unclear. Non-specific infection was reported as a possible risk factor associated with the event. The subject was discharged from the hospital on 02 July same year*.

Hepatic function abnormal was reported as resolved on 08 August same year*.

Approximately 10 months after randomization to standard of care in Study 20120138, on 16 January one year after*, the subject developed back and abdomen pain. He went to the emergency department where a computed tomography (CT) scan showed coeliac artery

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dissection). On the same day, the subject was hospitalized. The subject's laboratory tests showed WBC 7.70 x 10e3/ul, hemoglobin 15.7 g/dl, hematocrit 47.1 %, platelet count 31.0 x 10e4/ul, prothrombin time 11.1 seconds, international normalised ratio 0.93, and activated partial thromboplastin time 27.3 seconds. The subject and physician decided not to perform a surgical repair. The subject was started with nicardipine for hypertension control (blood pressure ranged from 130/100 mmHg to 150/100 mmHg). On 21 January one year after*, laboratory tests included hemoglobin 15.2 g/dl, hematocrit 45.7 %, and platelet count 31.1 x 10e4/ul. On 22 January one year after*, the subject's electrocardiogram and echocardiography were normal. The subject was treated with Exforge (amlodipine/ valsartan) and iopamidol. On 23 January one year after*, CT scan was negative for aortic aneurysm. The artery dissection was reported as ongoing.

The subject did not receive evolocumab prior to the events. The subject continued in the standard of care arm of Study 20120138.

The investigator reported that there was not a reasonable possibility that the events of hepatic function abnormal and artery dissection were related to study participation.

Date	AST (IU/L) (Normal range: 5-40)	ALT (IU/L) (Normal range: 4-45)	LDH (IU/L) (Normal range: 115-250)
20 March same year* Baseline	33	46	192
19 June same year*	146	134	379
23 June same year*	153	262	408
10 July same year*	40	56	187
07 August same year*	25	37	Not reported

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study: Study 20120122, Placebo SC QM + Atorvastatin QD 5 mg Year 1 treatment: Standard of Care
Report: Deep neck abscess

Subject [redacted] was a 65-year-old Asian woman participating in Study 20120138 who developed deep neck abscess.

The subject's medical history included type 2 diabetes mellitus, hyperlipidemia, dyslipidemia, cholelithiasis, chronic gastroenteritis, anxiety, and insomnia. Concomitant medications included glicazide, sitagliptin, zolpidem, ursodeoxycholic, hyoscine and alprazolam. Previous treatment for dyslipidemia and hyperlipidemia was rosuvastatin.

The subject received placebo in the parent study from 28 November one year ago* to 23 January same year*, and was randomized to standard of care in Study 20120138 on 11 March [redacted].

Approximately 1.5 months after the first dose of study treatment in Study 20120138, on 29 April same year*, the subject presented with throat swelling and was diagnosed with deep neck abscess. Treatment medications included cefditoren and carbocisteine. The subject was hospitalized the following day, on 30 April same year* and underwent throat surgery for deep neck abscess on 02 May same year*. Additional treatment medications included clindamyacin, cefazolin, and levofloxacin. The standard of care treatment was withheld during 01-06 May same year*.

Deep neck abscess was reported as resolved on 13 May same year* and the subject was discharged from the hospital on the same day. The subject stated that there were no malignant findings from the post-operative pathology report.

The subject resumed participation in the 1-year standard of care arm in Study 20120138 on 07 May same year*. As of the data cutoff date [redacted], the subject was continuing dosing in the study.

The investigator reported that there was not a reasonable possibility that the event of deep neck abscess was related to study participation.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study: Study 20120122, Evolocumab SC Q2W 140 mg + Atorvastatin QD 20 mg Year 1 treatment: Evolocumab SC Q2W 140 mg + Standard of Care
Report: Large intestine polyp

Subject [redacted] was a 63-year-old Asian woman participating in Study 20120138 who developed large intestine polyp.

The subject's medical history included type 2 diabetes mellitus, gastro-esophageal reflux disorder, gastric ulcer, dyslipidemia, and right knee injury. Concomitant medications included voglibose, nateglinide, metformin, rebamipide, loxoprofen, and lansoprazole.

Previous treatment for dyslipidemia was atorvastatin; ongoing treatment was atorvastatin.

The subject received evolocumab in the parent study from 26 November one year ago* to 04 February same year*, and was randomized to evolocumab in Study 20120138 and received the first dose on 04 March [redacted].

Approximately 2.5 months after the first dose of evolocumab in Study 20120138, on 28 May same year*, the subject developed a large intestine polyp. She was hospitalized on the same day and underwent endoscopy and polypectomy procedures. Treatment medications included flunitrazepam, carbazochrome, magnesium, hyoscine, pethidine, domperidone, and dimeticone. The pathology report was negative for malignancy.

The large intestine polyp was reported as resolved on 29 May same year* and the subject was discharged from the hospital on the same day.

The subject's last dose of evolocumab prior to the event was on 21 May same year*. The subject continued in the 1-year evolocumab arm in Study 20120138. As of the data cutoff date of [redacted], the subject was continuing dosing in the study.

The investigator reported that there was not a reasonable possibility that the event of large intestine polyp was related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study: Study 20120122, Placebo SC Q2W + Atorvastatin QD 20 mg Year 1 treatment: Evolocumab SC QM 420 mg + Standard of Care
Report: Ischemic enterocolitis

Subject [redacted] was a 59-year-old Asian woman participating in Study 20120138 who developed ischemic enterocolitis.

The subject's medical history included type 2 diabetes mellitus, hypertension, gastro-esophageal reflux disorder, dyslipidemia, and hypercholesterolemia. Concomitant medications included amoxicillin, metformin, candesartan, alogliptin, cilnidipine, esomeprazole, sodium alginate, rabeprazole, mosapride, and loratadine.

Previous treatment for dyslipidemia and hypercholesterolemia was rosuvastatin and atorvastatin; ongoing treatment was rosuvastatin.

The subject received placebo in the parent study from 11 December one year ago* to 17 February same year* and was randomized to evolocumab in Study 20120138 and received the first dose on 19 March [redacted].

Approximately 1 month after the first dose of evolocumab in Study 20120138, on 24 April same year*, the subject developed ischemic enterocolitis. The subject visited a dental clinic on 16 April same year* for the treatment of acute periodontitis and was prescribed a 7-day course of amoxicillin. Six days later on 22 April same year*, the subject experienced a decrease in appetite and on 24 April same year* the subject had bloody stool. The subject was hospitalized on 26 April same year* and two days later underwent gastro-intestinal endoscopy which showed inflammation from ascending colon to sigmoid colon. The subject was diagnosed with ischemic enterocolitis.

Laboratory results reported for 26 April same year* and 28 April same year* showed decreases in hemoglobin from 14.8 g/dL to 12.8 g/dL, C-reactive protein from 1.5 mg/dL to 0.7 mg/dL, and white blood cell count from 201.4 to 75.6 (units not provided). The subject's platelet count for both days was within normal limits.

The subject was discharged from the hospital on 01 May same year*. Ischemic enterocolitis resolved on 07 May same year*.

*新薬承認情報提供時に置き換え

The subject's last dose of evolocumab prior to the event was on 16 April same year*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing dosing in the study.

The investigator reported that there was not a reasonable possibility that the event of ischemic enterocolitis was related to evolocumab.

*新薬承認情報提供時に置き換え

No: [redacted]
Treatments: Parent study: Study 20120122, Placebo SC QM + Atorvastatin QD 20 mg Year 1 treatment: Standard of Care
Report: Adenomatous polyposis

Subject [redacted] was a 72-year-old Asian man participating in Study 20120138 who developed adenomatous polyposis.

The subject's medical history included adenomatous polyposis, hypertension, mixed dyslipidemia, primary hyperlipidemia, chronic gastritis, anxiety, benign prostatic hyperplasia, vertigo, chronic nasopharyngitis, hypothyroidism, constipation, allergic rhinitis, herniated disc, shoulder pain, bilateral leg pain, and former smoker.

Concomitant medications included delapril, hydroxyzine, lornoxicam, limaprost, betahistine, difenidol, sucralfate, roxatidine, ambroxol, epinastine, nifedipine, carbocisteine, azulene, epinastine, nifedipine, glycerol, candesartan, mometasone, pranlukast, levothyroxine, ketoprofen, imidafenacin, teprenone, imipramine, mirabegron, and sodium picosulfate.

Previous treatment for mixed dyslipidemia and primary hyperlipidemia was atorvastatin; ongoing treatment was atorvastatin.

The subject received placebo in the parent study from 12 December one year ago* to 06 February same year*, and was randomized to standard of care in Study 20120138 on 17 March [redacted].

Approximately 1 month after the first dose of study treatment in Study 20120138, on 28 April same year*, the subject had positive fecal occult blood test. On 23 May same year* the subject underwent colonoscopy which showed adenomatous polyposis group 3.

On 21 August same year*, the subject was hospitalized for a scheduled polypectomy the following day. The post-operative pathology report confirmed adenomatous polyposis group 3. Treatment medications included dimeticone, pethidine, diazepam, sodium picosulfate, carbazochrome and ribavirin.

Adenomatous polyposis was resolved on 22 August same year* and the subject was discharged from the hospital on 25 August same year*.

The subject continued the 1-year standard of care arm in Study 20120138. As of the data cutoff date of [redacted], the subject was continuing dosing in the study.

*新薬承認情報提供時に置き換え

The investigator reported that there was not a reasonable possibility that the event of adenomatous polyposis was related to study participation.

2.7.6.25 20120356 試験

治験課題名：原発性高コレステロール血症又は混合型脂質異常症患者の被験者が自宅で 3.5 mL パーソナルインジェクター又はペン型プレフィルドオートインジェクターを使用し evolocumab を全量投与できることを評価する無作為化多施設共同試験

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、その他米国及びカナダの 22 施設の医師

1.2 治験実施医療機関

[redacted]（米国[redacted]）、その他 22 施設

1.3 治験期間

[redacted]年[redacted]月[redacted]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 III 相

1.5 目的

1.5.1 主要目的

自宅でパーソナルインジェクター（AMD）又はペン型プレフィルドオートインジェクター（AI/pen）を用いて evolocumab 420 mg を使用者が全量投与できることを評価する。

1.5.2 副次目的

指定された医療機器を用いた evolocumab の低比重リポ蛋白コレステロール（LDL-C）への効果を評価する。

1.6 治験方法

本試験では、無作為化前に皮下（SC）投与の忍容性を確認する 4 週間のスクリーニング期を設け、AI/pen によりプラセボ 1.0 mL を 3 回投与した後、164 例の被験者を無作為に割り付け登録した。スクリーニング期のプラセボ投与は、被験者の意向に従って、被験者又は治験実施医療機関の職員が AI/pen を用いて実施した。最終的に組み入れ可能な被験者を evolocumab 420 mg の AMD（3.5 mL を 9 分間かけて単回投与）又は AI/pen（1 回につき 140 mg の用量を 30 分以内に 1.0 mL ずつ 3 回投与）

による SC 投与群に 1:1 の割合で無作為に割り付けた。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）を因子とする層別割り付けを用いた。

被験者は、初回投与日（Day1）に AMD 又は AI/pen の投与訓練（実施医療機関の職員の実演により、医療機器ごとに確立された取扱説明書を用いて実施）を受けた後、実施医療機関における監督下で AI/pen 又は AMD のいずれかを用いて evolocumab 420 mg を自ら SC 投与し、その後の投与 4 週時及び 8 週時は、自宅にて自己投与した。実施医療機関の職員は、投与 4 週時及び 8 週時の各来院時（電話連絡）に、被験者が問題なく evolocumab（AI/pen ; 1.0 mL の 3 回投与、AMD ; 3.5 mL の単回投与）を全量投与することができたかを質問し、その回答を電子症例報告書（eCRF）に記録した。被験者は LDL-C 測定のため、投与 10 週時に実施医療機関に来院し、投与 12 週時の LDL-C 測定及び追跡調査（来院）をもって試験終了（EOS）とした（治験薬の最終投与からおよそ 28 日後）。

本試験の評価スケジュールを以下の表 2.7.6.25-1 に示す。

表 2.7.6.25-1　評価スケジュール

Study Day / Time Point	Screen-ing	D1[a] Visit	W4 Telephone Visit	W8 Telephone Visit	W10 Visit	W12 Visit
General Procedures						
Informed consent	X					
Medical history	X					
Vital signs (sitting BP, heart rate)	X	X			X	X
Review for adverse events/ DRAEs/ serious adverse events/ CV events	X[b]	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X
Dietary instruction	X	X	X	X		X
Physical exam	X					X
Body height	X					
Body weight, waist circumference		X				X
ECG	X					
Randomization to IP		X[c]				
Central Laboratory						
Fasting lipids	X[c]	X			X	X
Chemistry	X[d]	X			X	X
Hematology	X	X			X	X
Hemoglobin A1c	X					
Thyroid-stimulating hormone	X					
Anti-evolocumab antibodies		X				X
Pharmacokinetics/PCSK-9		X			X	X
Hepatitis C virus antibodies	X[e]					
Hepatitis C virus viral load		X[e]				X[e]
Serum pregnancy; follicle-stimulating hormone[f]	X[g]					
Urinalysis		X				
Urine pregnancy[h]		X[h]				X[h]
Placebo injection	X					
Automated mini-doser or AI/Pen instruction	X	X	X	X		
Investigational product						
SC IP on-site		X				
SC IP non-clinic setting			X	X		
SC IP dispense		X				
SC IP reconcile					X	X
Site Administered questionnaire (eCRF)						
Inquiry re: administration of IP			X	X		

AI = ペン型プレフィルドオートインジェクター、BP = 血圧、CV = 心血管系、DRAEs =機器に関連した有害事象、ECG = 心電図、eCRF = 電子症例報告書、IP = 治験薬、PCSK9 = プロ蛋白転換酵素サブチリシン／ケキシン 9 型、SC = 皮下、W4 = week 4、W8 = week 8、W10 = week 10、W12 = week 12

[a] D1 = day of first administration of IP; a visit window of ± 2 days applied to all other visits

[b] Only adverse events possibly related to study procedures and serious adverse events were collected during the screening period.

[c] Randomization should have occurred within 5 - 10 days after obtaining the end of screening safety labs used to determine eligibility.

[d] Included fasting glucose

[e] Hepatitis C virus antibodies only in high risk subjects or in subjects with a history of hepatitis C virus or if alanine aminotransferase or aspartate aminotransferase > 2x upper limit of normal at any time during screening; viral load only in subjects positive for hepatitis C virus.

[f] Serum pregnancy in females of childbearing potential, follicle-stimulating hormone only if applicable per exclusion.

[g] Blood draw for chemistry and serum pregnancy (females of childbearing potential only) by central laboratory was required. These laboratory results applied to relevant exclusion criteria.

[h] Urine pregnancy in females of childbearing potential

1.7　被験者数

予定された被験者は 140 例（各投与群 70 例）であり、本試験にて無作為割り付けを行った症例は 164 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 18 歳以上 80 歳以下の、スクリーニング時の空腹時 LDL-C が 85 mg/dL（2.2 mmol/L）以上かつ空腹時トリグリセリドが 400 mg/dL（4.5 mmol/L）以下の男女とした。更に被験者は、無作為割り付け前 4 週間以上にわたり安定した用量でスタチン（HMG-CoA 還元酵素阻害薬）の投与を受けている（エゼチミブの併用有無にかかわらず）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、無菌、防腐剤を含有しない溶液として、固定用量の evolocumab の SC 投与用として単回使用、使い捨ての AMD 又は手持ち式、バネ式 AI/pen に充填されて供給された。

充填済みカートリッジ装着式の AMD は、単回使用、使い捨て、電気機械による身体装着型の医療機器であり、充填済み Crystal Zenith カートリッジと一緒に梱包されている。カートリッジの内容物は [redacted] mmol/L [redacted]、[redacted] mmol/L [redacted]、[redacted]%（w/v）[redacted] で調製された pH [redacted] の evolocumab 120 mg/mL 溶液であり、3.5 mL が投与できるように充填されていた。AMD は、約 9 分間で総用量 420 mg の evolocumab を単回 SC 投与するためにデザインされた。

AI/pen の内容物は、[redacted] mmol/L [redacted]、[redacted] mmol/L [redacted]、[redacted]%（w/v）[redacted] で調製された pH [redacted] の evolocumab 140 mg/mL 溶液であり、1.0mL が投与できるように充填されていた。AI/pen は、総用量 420 mg の evolocumab が異なる 3 カ所の皮下に投与された。AI/pen の投与時間は、1 回あたり約 15 秒間とした。

スクリーニング期に投与したプラセボは、[redacted]%（w/v）[redacted]、[redacted] mmol/L [redacted]、[redacted] mmol/L [redacted]、[redacted]%（w/v）[redacted] で調整された pH [redacted] の溶液であり、1.0 mL が投与可能な液量が、同様に AI/pen に充填されていた。

1.9.2　対照薬

該当なし

1.10　投与期間

4 週間のスクリーニング期（全被験者にプラセボを投与）と、無作為割り付け及び 12 週間の投与期間を設定し、全治験期間を最長 16 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4週時点及び8週時点における被験者の自己申告による全量投与の試みについても報告。治験薬を中止した被験者は、「治験薬投与前に投与を中止した」として記録した。すなわち、各人の主要評価項目は3つの回答（はい／いいえ／治験薬投与前の投与中止）のいずれかとなる。

1.11.2 副次評価項目

投与10週時点及び12週時点の平均値におけるLDL-Cのベースラインからの変化率

1.11.3 探索的評価項目

以下の判定された事象の発現率

- 全死因による死亡
- 心血管系疾患に起因する死亡
- 心筋梗塞
- 不安定狭心症のための入院
- 冠動脈の血行再建
- 脳卒中
- 一過性脳虚血発作（TIA）
- 心不全のための入院

1.12 統計手法

被験者の内訳、人口統計学的データ、ベースライン特性、曝露量、薬物動態データの特定の項目について記述統計量を示した。連続変数の要約統計量は、平均値、中央値、標準偏差（SD）又は標準誤差（SE）、最小値及び最大値などであり、カテゴリカル変数に関しては、頻度及び割合を示した。

全量投与に関する質問に対する被験者の回答（はい／いいえ／治験薬投与前の投与中止）についてそれぞれの投与ごとで割合を示した。治験薬を中止していないこと、治験薬の投与を試みたことを算出の条件とした。また、2回のVISITを通して取り得る回答のパターンごとの割合も示した。各投与群及び投与群間の割合の差について、95%信頼区間（CI）を算出した。

投与10週時点及び12週時点の平均におけるLDL-Cのベースラインからの変化率は、層別因子、投与群、時期、投与群と時期の交互作用項を含めた反復測定の混合効果モデルを用いて投与群ごとに推定した。各投与群及び平均値における投与群間の差について、95% CIを算出した。

別途指定しない限り、LDL-C に関連するすべての解析について再測定法を用いた。この方法では、算出LDL-Cが40 mg/dL（1.0 mmol/L）未満又はトリグリセリドが400 mg/dL（4.5 mmol/L）超えの基準に該当しない場合は算出LDL-Cを用い、該当する場合はUC LDL-Cの測定値を用いた。

治験中に発現した有害事象は、治験薬の初回投与後各被験者のEOSまでに発現したすべての有害事象と定義し、ICH国際医薬用語集（MedDRA）バージョン16.1を用いて全有害事象を器官別大分類及び基本語にコード化した。治験中に発現した有害事象、重篤な有害事象及び治験薬の投与中止に至った有害事象の発現率を器官別大分類及び基本語別に集計した。

治験中に発現した有害事象の要約は、頻度の高い順に投与群ごとに示した。ほかの脂質低下療法と関連する可能性のある有害事象、ほかのタンパク質注射剤の投与と関連する有害事象及びプロ蛋白転換酵素サブチリシン／ケキシン9型（PCSK9）阻害剤／LDL受容体の発現増加と理論的に関連のある有害事象（C型肝炎の有害事象）の発現率をカテゴリー及び基本語別に集計した。

本治験総括報告書では、医療機器に起因する副作用（有害事象のうち、治験担当医師が医療機器との関連が否定できないと判断した例）は、医療機器関連有害事象（DRAEs）として記載した。医療機器関連有害事象は、取扱説明書の記載が不十分であったために生じた有害事象、医療機器の機能不良、使用法過誤又は企図的誤用として要約した。

死亡、心筋梗塞、不安定狭心症のための入院、冠動脈の血行再建、脳卒中、一過性脳虚血発作及び心不全のための入院の有害事象は、独立臨床事象判定委員会により評価した。

治験期間を通した臨床検査パラメータ及びバイタルサインの結果を要約した。

いずれかの時点で抗evolocumab抗体産生が認められた被験者の数及び割合を示した。

2. 結果の要約

2.1 被験者の内訳

米国及びカナダの22施設において、合計164例の被験者が登録され、82例ずつAMD群又はAI/pen群のいずれかに無作為に割り付けられた。164例全例が予定された3回のうちの1回以上のevolocumab 4週間に1回のSC投与を受け、これらの被験者を最大の解析対象集団（FAS）とした。157例（95.7%）（AMD群 81例［98.8%］、AI/pen群 76例［92.7%］）が治験薬の投与を完了した。

被験者の内訳を表2.7.6.25-2に示す。

表 2.7.6.25-2　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）

被験者の状況	EvoMab AMD (N = 82) n (%)	EvoMab 3 x AI/pen (N = 82) n (%)	合計 (N = 164) n (%)
治験薬の状況			
投与を全く受けなかった被験者数	0 (0.0)	0 (0.0)	0 (0.0)
投与を受けた被験者数	82 (100.0)	82 (100.0)	164 (100.0)
投与完了	81 (98.8)	76 (92.7)	157 (95.7)
投与中止	1 (1.2)	6 (7.3)	7 (4.3)
有害事象	0 (0.0)	1 (1.2)	1 (0.6)
被験者の希望	1 (1.2)	2 (2.4)	3 (1.8)
追跡不能	0 (0.0)	3 (3.7)	3 (1.8)
試験完了の状況			
試験を完了した被験者	80 (97.6)	77 (93.9)	157 (95.7)
試験を中止した被験者	2 (2.4)	5 (6.1)	7 (4.3)
同意撤回	1 (1.2)	0 (0.0)	1 (0.6)
追跡不能	1 (1.2)	5 (6.1)	6 (3.7)

AI/pen = ペン型プレフィルドオートインジェクター、AMD = パーソナルインジェクター、 EvoMab = evolocumab、IP = 治験薬、N = 無作為割付けされた被験者数、n = 測定値を有する被験者数

Source: Modified from 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 52.4%が男性、47.6%が女性であり、被験者の平均年齢（SD）は 59.7（10.2）歳であった。大部分の被験者（64.6%）は 65 歳未満であった。白人（87.8%）が集団の大部分を占めており、次いで黒人（4.9%）、アジア人（4.3%）、アメリカ先住民又はアラスカ先住民（1.2%）、その他（1.2%）、混血（0.6%）であった。大部分の被験者（93.9%）が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 2.7.6.25-3 に示す。

表 2.7.6.25-3　ベースライン時の人口統計学的データ（FAS）

	EvoMab AMD (N = 82)	EvoMab AI/Pen (N = 82)	合計 (N = 164)
性別- n (%)			
男性	43 (52.4)	43 (52.4)	86 (52.4)
女性	39 (47.6)	39 (47.6)	78 (47.6)
民族- n (%)			
ヒスパニック又はラテン系	4 (4.9)	6 (7.3)	10 (6.1)
非ヒスパニック又はラテン系	78 (95.1)	76 (92.7)	154 (93.9)
人種- n (%)			
アメリカンインディアン又はアラスカ先住民	1 (1.2)	1 (1.2)	2 (1.2)
アジア人	4 (4.9)	3 (3.7)	7 (4.3)
黒人又はアフリカ系アメリカ人	6 (7.3)	2 (2.4)	8 (4.9)
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)
白人	69 (84.1)	75 (91.5)	144 (87.8)
その他	2 (2.4)	0 (0.0)	2 (1.2)
混血	0 (0.0)	1 (1.2)	1 (0.6)
日本人	0 (0.0)	0 (0.0)	0 (0.0)
第 1 世代	0 (0.0)	0 (0.0)	0 (0.0)
第 2 世代	0 (0.0)	0 (0.0)	0 (0.0)
第 3 世代	0 (0.0)	0 (0.0)	0 (0.0)
年齢 (歳)			
N	82	82	164
平均	60.1	59.2	59.7
SD	10.5	10.0	10.2
中央値	60.5	60.0	60.0
Q1, Q3	54.0, 69.0	52.0, 66.0	53.0, 68.0
最小, 最大	26, 80	34, 80	26, 80
年齢- n (%)			
< 65 歳	49 (59.8)	57 (69.5)	106 (64.6)
≥ 65 歳	33 (40.2)	25 (30.5)	58 (35.4)

AI/pen = ペン型プレフィルドオートインジェクター、N = 無作為割付けし治験薬を投与した被験者数、EvoMab = evolocumab (AMG 145)、Q1 = 25 パーセンタイル、Q3 =75 パーセンタイル、SD =標準偏差

[redacted]

2.3　有効性の結果

投与4週時点及び8週時点における自己投与でのevolocumabの全量投与例は、AMD群93.9%（77例）、AI/pen群91.5%（75例）であり（表2.7.6.25-4）、被験者の割合におけるAI/pen群とAMD群の差（95% CI）は-2.4%（-11.2%、6.1%）であった。予定された来院期間外に全量投与を行った2例の被験者を含めた場合、2回の全量投与を行った被験者の割合は、AMD群95.1%（78例）、AI/pen群92.7%（76例）であり、群間差は-2.4%（-10.7%、5.6%）であった。全体として、AMD群の97.6%（80例）及びAI/pen群の95.1%（78例）の被験者が自宅で問題なくevolocumabを1回以上投与することができた。

AMD群の1例（1.2%）及びAI/pen群の4例（4.9%）が投与8週時点までに治験薬投与を中止した。投与中止以外の理由により、AMD群の4例（4.9%）及びAI/pen群の2例（2.4%）が投与4週時点でevolocumabを全量投与することができず、各群の2例（2.4%）が投与8週時点でevolocumabを全量投与することができなかった。週別の投与解析では、AMDによってevolocumabを全量投与した被験者の割合（95% CI）は、投与4週時点で95.1%（88.1%、98.1%）、投与8週時点で96.3%（89.8%、98.7%）であり、1例（1.2%［0.2%、6.6%］）が予定された来院期間外に全量投与を行った。AI/pen群では、evolocumabを全量投与した被験者の割合（95% CI）は、投与4週時点で93.9%（86.5%、97.4%）、投与8週時点で92.7%（84.9%、96.6%）であり、1例（1.2%［0.2%、6.6%］）が予定された来院期間外に全量投与を行った。

表 2.7.6.25-4　投与 4 週及び 8 週時点における治験薬全量投与に関する被験者の自己申告結果（FAS）

	EvoMab AMD (N = 82)	EvoMab 3 x AI/pen (N = 82)	治療差
すべての自宅投与の要約			
全量自宅投与少なくとも 1 回- n (%)	80 (97.6)	78 (95.1)	-2.4
(95% CI)	(91.5, 99.3)	(88.1, 98.1)	(-9.7, 4.3)
week 4 - n (%)	78 (95.1)	77 (93.9)	-1.2
(95% CI)	(88.1, 98.1)	(86.5, 97.4)	(-9.2, 6.6)
week 8 - n (%)	79 (96.3)	76 (92.7)	-3.7
(95% CI)	(89.8, 98.7)	(84.9, 96.6)	(-11.8, 4.0)
計画外 week - n (%)	1 (1.2)	1 (1.2)	0.0
(95% CI)	(0.2, 6.6)	(0.2, 6.6)	(-5.5, 5.5)
全量自宅投与少なくとも 2 回- n (%)	78 (95.1)	76 (92.7)	-2.4
(95% CI)	(88.1, 98.1)	(84.9, 96.6)	(-10.7, 5.6)
計画 weeks - n (%)	77 (93.9)	75 (91.5)	-2.4
(95% CI)	(86.5, 97.4)	(83.4, 95.8)	(-11.2, 6.1)
計画外 week に 1 回- n (%)	1 (1.2)	1 (1.2)	0.0
(95% CI)	(0.2, 6.6)	(0.2, 6.6)	(-5.5, 5.5)
Week 4 の結果			
被験者の状況			
全量投与 n (%)	78 (95.1)	77 (93.9)	-1.2
(95% CI)	(88.1, 98.1)	(86.5, 97.4)	(-9.2, 6.6)
全量投与せず n (%)	4 (4.9)	2 (2.4)	-2.4
(95% CI)	(1.9, 11.9)	(0.7, 8.5)	(-9.7, 4.3)
治験薬中止 n (%)	0 (0.0)	3 (3.7)	3.7
(95% CI)	(0.0, 4.5)	(1.3, 10.2)	(-1.4, 10.2)
Week 8 の結果			
被験者の状況			
全量投与 n (%)	79 (96.3)	76 (92.7)	-3.7
(95% CI)	(89.8, 98.7)	(84.9, 96.6)	(-11.8, 4.0)
全量投与できず n (%)	2 (2.4)	2 (2.4)	0.0
(95% CI)	(0.7, 8.5)	(0.7, 8.5)	(-6.3, 6.3)
治験薬中止 n (%)	1 (1.2)	4 (4.9)	3.7
(95% CI)	(0.2, 6.6)	(1.9, 11.9)	(-2.5, 10.7)

AI/pen = ペン型プレフィルドオートインジェクター、AMD =パーソナルインジェクター、CI = 信頼区間、EvoMab = evolocumab、IP = 治験薬、N = 無作為割付けし治験薬を投与した被験者数、n = 測定値を有する被験者数

全量投与とは計画した投与時点での全量投与の記録がある場合。

全量投与できずとは計画した投与時点で治験薬を中止していないが全量投与の記録がない場合。治験薬の中止とは計画した投与時点前に被験者が治験薬の投与を中止した記録がある場合。

95% CI は Wilson score 法を用いて算出した。治療差の 95% CI の割合は Newcombe hybrid score 法を用いて算出した。

[redacted]

表 2.7.6.25-4　投与 4 週及び 8 週時点における治験薬全量投与に関する被験者の自己申告結果（FAS）（続き）

	EvoMab AMD (N = 82)	EvoMab 3 x AI/pen (N = 82)	治療差
Week 4 及び 8			
被験者の状況			
Week 4 全量投与及び			
Week 8 全量投与 n (%)	77 (93.9)	75 (91.5)	-2.4
(95% CI)	(86.5, 97.4)	(83.4, 95.8)	(-11.2, 6.1)
Week 8 に 全量投与できず n (%)	1 (1.2)	2 (2.4)	1.2
(95% CI)	(0.2, 6.6)	(0.7, 8.5)	(-4.4, 7.3)
Week 8 治験薬中止 n (%)	0 (0.0)	0 (0.0)	0.0
(95% CI)	(0.0, 4.5)	(0.0, 4.5)	(-4.5, 4.5)
Week 4 に全量投与できず			
Week 8 全量投与 n (%)	2 (2.4)	1 (1.2)	-1.2
(95% CI)	(0.7, 8.5)	(0.2, 6.6)	(-7.3, 4.4)
Week 8 に全量投与できず n (%)	1 (1.2)	0 (0.0)	-1.2
(95% CI)	(0.2, 6.6)	(0.0, 4.5)	(-6.6, 3.4)
Week 8 治験薬中止 n (%)	1 (1.2)	1 (1.2)	0.0
(95% CI)	(0.2, 6.6)	(0.2, 6.6)	(-5.5, 5.5)
Week 4 治験薬中止し			
Week 8 治験薬中止 n (%)	0 (0.0)	3 (3.7)	3.7
(95% CI)	(0.0, 4.5)	(1.3, 10.2)	(-1.4, 10.2)

AI/pen = ペン型プレフィルドオートインジェクター、AMD =パーソナルインジェクター、CI = 信頼区間、EvoMab = evolocumab、IP = 治験薬、N = 無作為割付けし治験薬を投与した被験者数、n = 測定値のある被験者数

全量投与とは計画した投与時点での全量投与の記録がある場合。

全量投与できなかったとは計画した投与時点で治験薬を中止していないが全量投与の記録がない場合。治験薬の中止とは計画した投与時点前に被験者が治験薬の投与を中止した記録がある場合。

95% CI は Wilson score 法を用いて算出した。治療差の 95% CI の割合は Newcombe hybrid score 法を用いて算出した。

[redacted]

ベースライン時の平均 LDL-C 濃度（SD）は、AMD 群 115.3（27.0）mg/dL、AI/pen 群 117.3（23.9）mg/dL であった。投与 10 週時点及び投与 12 週時点の平均における reflexive LDL-C のベースラインからの低下率の最小二乗平均（SE）は、AMD 群 67.9%（2.4%）、AI/pen 群 64.5%（2.4%）であり、投与群差の推定値は 3.4%（3.2%）であった。アドホック解析では、投与 12 週時点の reflexive LDL-C のベースラインからの低下率（SE）は AMD 群 60.4%（1.9%）、AI/pen 群 60.4%（2.7%）と算出された。

2.4 薬力学の結果

ベースライン時の平均 PCSK9 濃度（SD）は AMD 群 303（81.3）ng/mL、AI/pen 群 311（96.1）ng/mL であった。evolocumab 投与後の平均非結合型 PCSK9 濃度（SD）は、AMD 群では投与 10 週時点で 40.4（89.6）μg/mL 及び投与 12 週時点で 251（116）μg/mL であり、AI/pen 群では投与 10 週時点で 35.7（68.2）μg/mL 及び投与 12 週時点で 230（127）μg/mL であった。

2.5 薬物動態の結果

薬物動態解析対象集団において evolocumab 420 mg QM を 8 週間 SC 投与したときの平均血清中非結合型 evolocumab 濃度（SD）は、AMD 群では投与 10 週時点で 29.1（18.1）μg/mL 及び投与 12 週時点で 7.5（6.2）μg/mL であり、AI/pen 群では投与 10 週時点で 32.9（21.0）μg/mL 及び投与 12 週時点で 10.3（8.8）μg/mL であった。血清中非結合型 evolocumab の平均濃度は投与 10 週時点（投与 2 週後）で最も高く、同時点で非結合型 PCSK9 濃度に顕著な低下が認められたことと相関関係が示された。

2.6 安全性の結果

2.6.1 有害事象

2.6.1.1 有害事象の要約

有害事象の要約を表 2.7.6.25-5 に示す。

表 2.7.6.25-5 有害事象の要約（FAS）

	EvoMab AMD (N = 82)	EvoMab 3 x AI/pen (N = 82)
有害事象発現例 - n(%)	21 (25.6)	27 (32.9)
Grade ≥ 2	6 (7.3)	9 (11.0)
Grade ≥ 3	1 (1.2)	1 (1.2)
Grade ≥ 4	0 (0.0)	0 (0.0)
重篤な有害事象	0 (0.0)	1 (1.2)
治験薬の投与中止	0 (0.0)	1 (1.2)
重篤	0 (0.0)	0 (0.0)
非重篤	0 (0.0)	1 (1.2)
死亡	0 (0.0)	0 (0.0)
機器に関連した有害事象	1 (1.2)	2 (2.4)
Grade ≥ 2	0 (0.0)	0 (0.0)
Grade ≥ 3	0 (0.0)	0 (0.0)
Grade ≥ 4	0 (0.0)	0 (0.0)
重篤な有害事象	0 (0.0)	0 (0.0)

AI/pen = ペン型プレフィルドオートインジェクター、AMD = パーソナルインジェクター、 EvoMab = evolocumab; IP = 治験薬、N = 無作為割付けし治験薬を投与した被験者数、n = 測定値のある被験者数

Source: Modified from Table 14-6.1.1

2.6.1.2　全有害事象

有害事象は、AMD 群で 25.6%、AI/pen 群で 32.9%に認められた。また、重篤な有害事象は AMD 群では認められず、AI/pen 群では 1 例に認められた。死に至った有害事象は認められなかった。治験担当医師によりいずれかの医療機器との関連が否定できないと判断された有害事象が 3 例に認められた。いずれも重篤な有害事象ではなかった。

治験中に発現した有害事象を器官別大分類及び基本語別に表 2.7.6.25-6 に示す。

また、治験薬投与と関連ありと判断された器官別大分類及び基本語別の有害事象を ISS の Table 14 6.604.11（日本語訳）（5.3.5.3 項）に示す。

表 2.7.6.25-6　治験中に発現した器官別大分類及び基本語別の有害事象（FAS）

器官別大分類 基本語	EvoMab AMD (N = 82) n (%)	EvoMab AI/Pen (N = 82) n (%)
有害事象発現例	21 (25.6)	27 (32.9)
耳および迷路障害	1 (1.2)	1 (1.2)
頭位性回転性めまい	0 (0.0)	1 (1.2)
耳痛	1 (1.2)	0 (0.0)
内分泌障害	1 (1.2)	0 (0.0)
甲状腺機能低下症	1 (1.2)	0 (0.0)
眼障害	1 (1.2)	1 (1.2)
白内障	0 (0.0)	1 (1.2)
緑内障	0 (0.0)	1 (1.2)
散瞳	1 (1.2)	0 (0.0)
胃腸障害	2 (2.4)	4 (4.9)

AI/pen = ペン型プレフィルドオートインジェクター、N = 無作為割付けし治験薬を投与した被験者数、
EvoMab = evolocumab (AMG 145)
MedDRA 16.1 版でコード化

[redacted]

表 2.7.6.25-6　治験中に発現した器官別大分類及び基本語別の有害事象（FAS）（続き）

器官別大分類 基本語	EvoMab AMD (N = 82) n (%)	EvoMab AI/Pen (N = 82) n (%)
胃腸障害（続き）		
腹痛	0 (0.0)	1 (1.2)
下腹部痛	0 (0.0)	1 (1.2)
胃食道逆流性疾患	0 (0.0)	1 (1.2)
小腸閉塞	0 (0.0)	1 (1.2)
上腹部痛	1 (1.2)	0 (0.0)
下痢	1 (1.2)	0 (0.0)
悪心	1 (1.2)	0 (0.0)
一般・全身障害および投与部位の状態	3 (3.7)	4 (4.9)
非心臓性胸痛	0 (0.0)	2 (2.4)
無力症	0 (0.0)	1 (1.2)
疲労	2 (2.4)	1 (1.2)
注射部位血腫	0 (0.0)	1 (1.2)

AI/pen = ペン型プレフィルドオートインジェクター、N = 無作為割付けし治験薬を投与した被験者数、
EvoMab = evolocumab (AMG 145)
MedDRA 16.1 版でコード化

[redacted]

表 2.7.6.25-6　治験中に発現した器官別大分類及び基本語別の有害事象（FAS）（続き）

器官別大分類 基本語	EvoMab AMD (N = 82) n (%)	EvoMab AI/Pen (N = 82) n (%)
一般・全身障害および投与部位の状態（続き）		
疼痛	0 (0.0)	1 (1.2)
注射部位反応	1 (1.2)	0 (0.0)
感染症および寄生虫症	7 (8.5)	6 (7.3)
胃腸炎	0 (0.0)	1 (1.2)
ウイルス性胃腸炎	0 (0.0)	1 (1.2)
帯状疱疹	1 (1.2)	1 (1.2)
腎感染	0 (0.0)	1 (1.2)
鼻咽頭炎	0 (0.0)	1 (1.2)
肺炎	0 (0.0)	1 (1.2)
尿路感染	0 (0.0)	1 (1.2)
気管支炎	2 (2.4)	0 (0.0)
蜂巣炎	1 (1.2)	0 (0.0)
口腔ヘルペス	1 (1.2)	0 (0.0)

AI/pen = ペン型プレフィルドオートインジェクター、N = 無作為割付けし治験薬を投与した被験者数、
EvoMab = evolocumab (AMG 145)
MedDRA 16.1 版でコード化

[redacted]

表 2.7.6.25-6　治験中に発現した器官別大分類及び基本語別の有害事象（FAS）（続き）

器官別大分類 基本語	EvoMab AMD (N = 82) n (%)	EvoMab AI/Pen (N = 82) n (%)
感染症および寄生虫症（続き）		
咽頭炎	1 (1.2)	0 (0.0)
副鼻腔炎	3 (3.7)	0 (0.0)
扁桃炎	1 (1.2)	0 (0.0)
傷害、中毒および処置合併症	0 (0.0)	3 (3.7)
動物咬傷	0 (0.0)	1 (1.2)
動物による引っかき傷	0 (0.0)	1 (1.2)
擦過傷	0 (0.0)	1 (1.2)
臨床検査	1 (1.2)	5 (6.1)
アラニンアミノトランスフェラーゼ増加	0 (0.0)	1 (1.2)
アスパラギン酸アミノトランスフェラーゼ増加	0 (0.0)	1 (1.2)
血中カルシウム増加	0 (0.0)	1 (1.2)

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AI/pen = ペン型プレフィルドオートインジェクター、N = 無作為割付けし治験薬を投与した被験者数、
EvoMab = evolocumab (AMG 145)
MedDRA 16.1 版でコード化

[redacted]

表 2.7.6.25-6　治験中に発現した器官別大分類及び基本語別の有害事象（FAS）（続き）

器官別大分類 基本語	EvoMab AMD (N = 82) n (%)	EvoMab AI/Pen (N = 82) n (%)
臨床検査（続き）		
血中クレアチンホスホキナーゼ増加	0 (0.0)	1 (1.2)
心雑音	0 (0.0)	1 (1.2)
頚動脈雑音	0 (0.0)	1 (1.2)
肝酵素上昇	0 (0.0)	1 (1.2)
白血球数増加	0 (0.0)	1 (1.2)
血中重炭酸塩減少	1 (1.2)	0 (0.0)
代謝および栄養障害	1 (1.2)	0 (0.0)
2 型糖尿病	1 (1.2)	0 (0.0)
筋骨格系および結合組織障害	2 (2.4)	7 (8.5)
四肢痛	0 (0.0)	3 (3.7)
関節痛	0 (0.0)	1 (1.2)

AI/pen = ペン型プレフィルドオートインジェクター、N = 無作為割付けし治験薬を投与した被験者数、
EvoMab = evolocumab (AMG 145)
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[redacted]

表 2.7.6.25-6　治験中に発現した器官別大分類及び基本語別の有害事象（FAS）（続き）

器官別大分類 基本語	EvoMab AMD (N = 82) n (%)	EvoMab AI/Pen (N = 82) n (%)
筋骨格系および結合組織障害（続き）		
背部痛	1 (1.2)	1 (1.2)
筋痙縮	0 (0.0)	1 (1.2)
頚部痛	0 (0.0)	1 (1.2)
腱炎	0 (0.0)	1 (1.2)
関節炎	1 (1.2)	0 (0.0)
神経系障害	3 (3.7)	2 (2.4)
浮動性めまい	1 (1.2)	1 (1.2)
片頭痛	0 (0.0)	1 (1.2)
失神	1 (1.2)	0 (0.0)
白質病変	1 (1.2)	0 (0.0)
精神障害	1 (1.2)	1 (1.2)
不安	0 (0.0)	1 (1.2)

AI/pen = ペン型プレフィルドオートインジェクター、N = 無作為割付けし治験薬を投与した被験者数、
EvoMab = evolocumab (AMG 145)
MedDRA 16.1 版でコード化

[redacted]

表 2.7.6.25-6　治験中に発現した器官別大分類及び基本語別の有害事象（FAS）（続き）

器官別大分類 基本語	EvoMab AMD (N = 82) n (%)	EvoMab AI/Pen (N = 82) n (%)
精神障害（続き）		
うつ病	1 (1.2)	0 (0.0)
腎および尿路障害	1 (1.2)	1 (1.2)
腎結石症	0 (0.0)	1 (1.2)
血尿	1 (1.2)	0 (0.0)
呼吸器、胸郭および縦隔障害	1 (1.2)	2 (2.4)
喘息	0 (0.0)	1 (1.2)
咳嗽	0 (0.0)	1 (1.2)
睡眠時無呼吸症候群	1 (1.2)	0 (0.0)
皮膚および皮下組織障害	1 (1.2)	1 (1.2)
アレルギー性皮膚炎	0 (0.0)	1 (1.2)

AI/pen = ペン型プレフィルドオートインジェクター、N = 無作為割付けし治験薬を投与した被験者数、
EvoMab = evolocumab (AMG 145)
MedDRA 16.1 版でコード化

[redacted]

表 2.7.6.25-6　治験中に発現した器官別大分類及び基本語別の有害事象（FAS）（続き）

器官別大分類 基本語	EvoMab AMD (N = 82) n (%)	EvoMab AI/Pen (N = 82) n (%)
皮膚および皮下組織障害（続き）		
皮膚線維症	1 (1.2)	0 (0.0)
血管障害	0 (0.0)	2 (2.4)
深部静脈血栓症	0 (0.0)	1 (1.2)
高血圧	0 (0.0)	1 (1.2)

AI/pen = ペン型プレフィルドオートインジェクター、N = 無作為割付けし治験薬を投与した被験者数、
EvoMab = evolocumab (AMG 145)
MedDRA 16.1 版でコード化

[redacted]

2.6.1.3　主な有害事象

全被験者の 5%（5 例）を超えて発現した有害事象はいずれの投与群にも認められなかった。最も多く認められた有害事象（AMD 群、AI/pen 群）は四肢痛（0%［0 例］、3.7%［3 例］）、疲労（2.4%［2 例］、1.2%［1 例］）、副鼻腔炎（3.7%［3 例］、0%［0 例］）であった。

2.6.1.4　医療機器の安全性

AMD 群で注射部位反応が 1 例（1.2%）に 2 件認められ、AI/pen 群で注射部位血腫、四肢痛が各 1 例（1.2%）に認められた。

2.6.1.5　有害事象による投与中止

治験薬の投与中止に至った有害事象は、AI/pen 群で注射部位血腫が 1 例（1.2%）に認められた。

2.6.1.6　死に至った有害事象

本試験において死亡例は認められなかった。

2.6.1.7　重篤な有害事象

重篤な有害事象は、AMD 群では認められず、AI/pen 群では 1 例（1.2%、深部静脈血栓症）に認められた。この重篤な有害事象は治験担当医師により治験薬と関連なしと判断された。

2.6.2　臨床検査値の評価と心電図

本試験では、特定の臨床検査項目、心電図及びバイタルサインにおいて、臨床的に重要かつ治験薬投与と関連がある異常変動は認められなかった。肝機能検査値又はクレアチンホスホキナーゼ値の異常により、事前に規定された治験薬投与の中止基準に該当した被験者はいなかった。

2.6.3　抗 evolocumab 抗体産生の状況

163 例（ベースライン時 163 例及びベースライン後 152 例）について、抗 evolocumab 抗体が陽性となった被験者は認められなかった。

3.　結論

本試験では、AMD（3.5 mL を 9 分間かけて単回 SC 投与）又は AI/pen（30 分以内に 1.0 mL ずつ 3 回投与）のいずれを用いても、被験者が投与訓練を実施後に自宅にて、4 週時及び 8 週時に evolocumab 420 mg 全量を問題なく自己投与できることを確認した。自己投与にて evolocumab を問題なく投与できる可能性は、AMD と AI/pen との間で類似していた。

投与 12 週時点における LDL-C のベースラインからの低下及び投与 10 週時点並びに投与 12 週時点の平均における LDL-C のベースラインからの低下は、evolocumab を自己投与で AMD 又は AI/pen のいずれかを用いて投与したときも臨床的に同様であった。また、evolocumab 420 mg SC 投与後の血清中非結合型 evolocumab 濃度及び血清中非結合型 PCSK9 濃度は、投与 10 週時点及び投与 12 週時点のいずれにおいても、AI/pen 群と AMD 群で同様であった。薬物動態及び薬力学データから、evolocumab はいずれの方法（AMD 又は AI/pen 3 本）を用いても、治療効果の面で臨床的に同程度であることが示された。

有害事象及び医療機器関連有害事象は、AMD 群と AI/pen 群との間に差は認められなかった。投与に問題がないとの患者からの報告に基づき、AMD 及び AI/pen は、安定した用量でスタチンの投与を受けている（エゼチミブの併用有無にかかわらず）原発性高脂血症及び混合型脂質異常症患者への evolocumab 自己投与の使用目的に適した医療機器であると考えられた。

本試験の結果から、安定した用量でスタチンの投与を受けている（エゼチミブの併用有無にかかわらず）原発性高脂血症及び混合型脂質異常症被験者で、自宅で問題なく自己投与できることが確認され、使用目的及び使用条件に関して、AMD 及び AI/pen の投与はいずれも有効かつ安全であり、忍容性は良好であった。

4. 有害事象の叙述

4.1 死亡、重篤な有害事象及び投与中止に至った有害事象の症例一覧

重篤な有害事象及び投与中止に至った有害事象を表 2.7.6.25-7 に示す。

表 2.7.6.25-7 死亡、重篤な有害事象及び投与中止に至った有害事象の要約

番号	被験者 ID	理由			MedDRA 基本語
		死亡	その他の重篤な有害事象	投与中止に至った有害事象	
1	[redacted]			X	注射部位血腫
2	[redacted]		X		深部静脈血栓症

MedDRA = ICH 国際医薬用語集

4.2 重篤な有害事象の叙述

重篤な有害事象の叙述は、下記に示す。

Subject No: [redacted]
Treatment: Evolocumab SC Q4W 420 mg
Report: Deep vein thrombosis

Subject [redacted] was a 51-year-old white man participating in Study 20120356 who developed deep vein thrombosis. The subject's medical history included hypercholesterolemia, normal systolic function (left ventricular ejection fraction ≥ 50%), hypertension, ex-smoker, trace bilateral ankle edema, hyperlipidemia, fusiform aneurysm of infrarenal aorta, trace mitral insufficiency, reflux, chronic obstructive pulmonary disease, back pain from trauma, hepatitis, obesity, and a family history of blood clots. The subject did not have a history of blood clots. Concomitant medications included acetylsalicylic acid, metoprolol, telmisartan, hydrochlorothiazide, famotidine, a combination of aluminium hydroxide gel and dried magnesium carbonate, hydrocodone, and paracetamol. Previous and current treatment for hypercholesterolemia included pitavastatin.

The subject received the first dose of evolocumab on 06 August [redacted]. Approximately 10 days later, on 16 August same year*, the subject developed swelling of the left leg and he noticed discoloration on his left leg. An ultrasound was performed and showed deep vein thrombosis in the femoral, popliteal, and lesser saphenous veins. On 20 August same year* the subject was hospitalized for further evaluation and treatment and he was started on a heparin drip and warfarin.

On an unspecified date, laboratory tests included factor V Leiden mutation negative andanti-cardiolipin immunoglobulin IgA, IgG, and IgM antibodies were all negative. Additional treatment included enoxaparin. The event of deep vein thrombosis was reported to have resolved on 22 August same year* and the subject was discharged from the hospital on the same date.

The subject's last dose of evolocumab prior to the event was on 06 August same year*. Evolocumab was continued. The subject's last dose of evolocumab in the study was on 01 October same year*. The subject completed the study on 29 October same year*. The investigator reported that there was not a reasonable possibility that the event of deep vein thrombosis was related to investigational product or the device.

*新薬承認情報提供時に置き換え