Report on the Deliberation Results

December 7, 2015

Evaluation and Licensing Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Repatha SC Injection 140 mg Syringe Repatha SC Injection 140 mg Pen
[Non-proprietary name]	Evolocumab (Genetical Recombination) (JAN*)
[Applicant]	Amgen Astellas BioPharma K.K.
[Date of application]	March 20, 2015

[Results of deliberation]
In the meeting held on November 27, 2015, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 8 years. Neither the drug substance nor the drug product is classified as a poisonous drug or a powerful drug. The product is classified as a biological product.

[Condition for approval]
The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

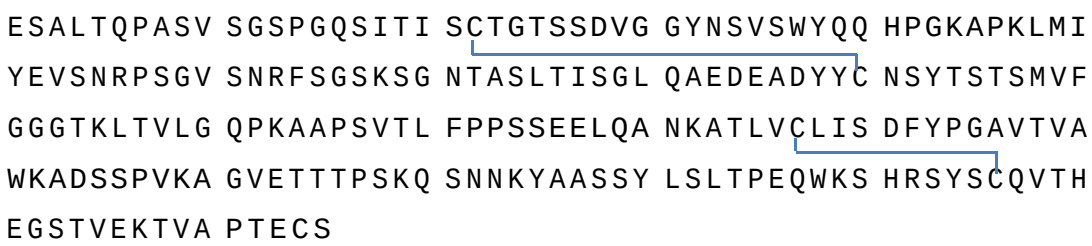
Review Report

November 9, 2015
Pharmaceuticals and Medical Devices Agency

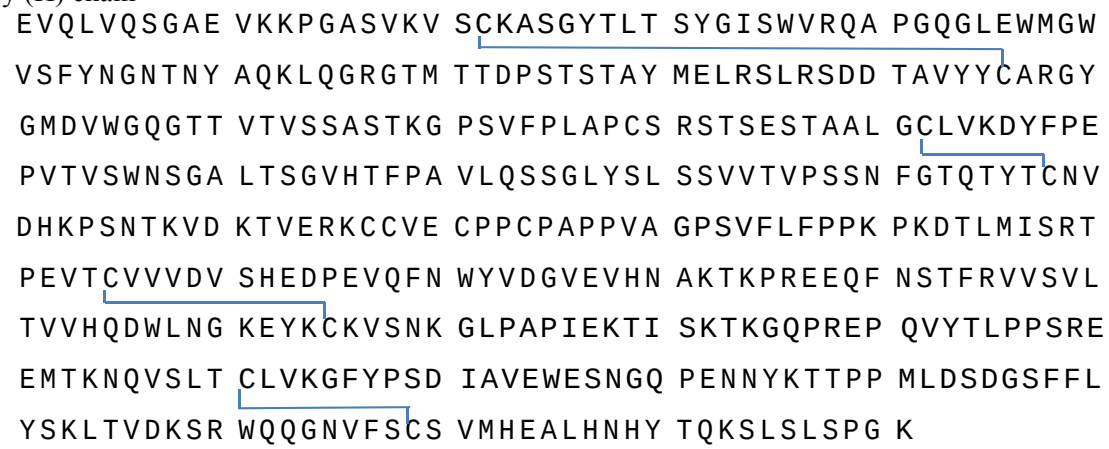
The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name]	(a) Repatha SC Injection 140 mg Syringe (b) Repatha SC Injection 140 mg Pen
[Non-proprietary name]	Evolocumab (Genetical Recombination)
[Applicant]	Amgen Astellas BioPharma K.K.
[Date of application]	March 20, 2015
[Dosage form/Strength]	(a) Solution for injection in a prefilled syringe: Each syringe (1 mL) contains 140 mg of Evolocumab (Genetical Recombination). (b) Solution for injection in a prefilled kit: Each kit (1 mL) contains 140 mg of Evolocumab (Genetical Recombination).
[Application classification]	Prescription drug, (1) Drug with a new active ingredient
[Definition]	Evolocumab is a recombinant human IgG2 monoclonal antibody against human proprotein convertase subtilisin/kexin type 9 (PCSK9). Evolocumab is produced in Chinese hamster ovary cells. Evolocumab is a glycoprotein (molecular weight: ca. 144,000) composed of 2 H-chains (γ2-chains) consisting of 441 amino acid residues each and 2 L-chains (λ-chains) consisting of 215 amino acid residues each.

[Chemical structure]
Light (L) chain



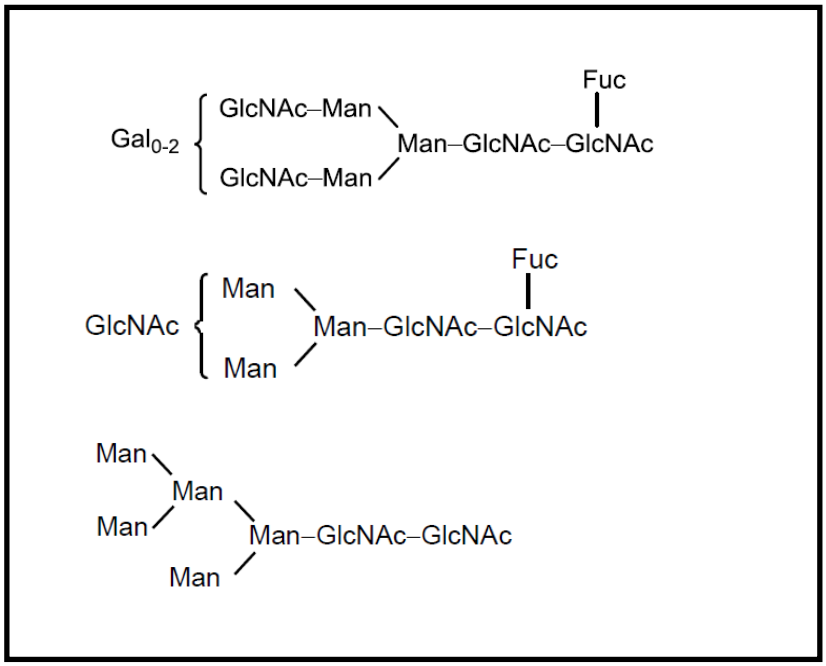
Heavy (H) chain



Glycosylation site: N291 in H chain
Partial processing: K441 in H chain

Disulfide bonds: C214 in L chain - C129 in H chain, C217 in H chain - C217 in H chain, C218 in H chain - C218 in H chain, C221 in H chain - C221 in H chain, C224 in H chain - C224 in H chain

Estimated main carbohydrate structures



Gal, Galactose; GlcNAc, N-acetylglucosamine; Man, Mannose; Fuc, Fucose

Molecular formula: $C_{6242}H_{9684}N_{1668}O_{1996}S_{56}$ (protein moiety consisting of 4 chains)
H chain: $C_{2140}H_{3313}N_{571}O_{664}S_{21}$
L chain: $C_{981}H_{1529}N_{263}O_{334}S_{7}$
Molecular weight: approximately 144,000

[Items warranting special mention] None
[Reviewing office] Office of New Drug II

Review Results

November 9, 2015

[Brand name]	(a) Repatha SC Injection 140 mg Syringe (b) Repatha SC Injection 140 mg Pen
[Non-proprietary name]	Evolocumab (Genetical Recombination)
[Applicant]	Amgen Astellas BioPharma K.K.
[Date of application]	March 20, 2015

[Results of review]
Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the efficacy of the product in the treatment of familial hypercholesterolemia (FH) and hypercholesterolemia has been demonstrated and its safety is acceptable in view of its observed benefits. The occurrences of adverse events related to hypersensitivity or immunogenicity and safety in patients with homozygous FH patients (including pediatric patients), the elderly patients (≥75 years of age), patients with hepatic impairment, and patients with hepatitis C virus (HCV) infection should be investigated in the post-marketing surveillance, etc.

As a result of its regulatory review, PMDA has concluded that the product may be approved for the indication and dosage and administration as shown below, with the following conditions.

[Indications]	Familial hypercholesterolemia, hypercholesterolemia The product should be used only in patients with high cardiovascular risk who have had an inadequate response to HMG-CoA reductase inhibitors.
[Dosage and administration]	Heterozygous familial hypercholesterolemia and hypercholesterolemia: The usual adult dosage of Evolocumab (Genetical Recombination) is 140 mg once every 2 weeks or 420 mg once every 4 weeks, administered as a subcutaneous injection. Homozygous familial hypercholesterolemia: The usual adult dosage of Evolocumab (Genetical Recombination) is 420 mg once every 4 weeks administered as a subcutaneous injection. Evolocumab 420 mg can be administered subcutaneously once every 2 weeks if an adequate response is not achieved. When used as an adjunct to LDL apheresis, Evolocumab may be started at a dose of 420 mg once every 2 weeks subcutaneously.
[Condition for approval]	The applicant is required to develop and appropriately implement a risk management plan.

Review Report (1)

September 17, 2015

I. Product Submitted for Registration

[Brand name]	(a) Repatha SC Injection 140 mg Syringe (b) Repatha SC Injection 140 mg Pen
[Non-proprietary name]	Evolocumab (Genetical Recombination)
[Applicant]	Amgen Astellas BioPharma K.K.
[Date of application]	March 20, 2015
[Dosage form/Strength]	(a) Solution for injection in a prefilled syringe: Each syringe (1 mL) contains 140 mg of Evolocumab (Genetical Recombination). (b) Solution for injection in a prefilled kit: Each kit (1 mL) contains 140 mg of Evolocumab (Genetical Recombination).
[Proposed indication]	Hypercholesterolemia and heterozygous familial hypercholesterolemia Homozygous familial hypercholesterolemia The product should be used only in patients who have had an inadequate response to conventional therapies.
[Proposed dosage and administration]	Hypercholesterolemia and heterozygous familial hypercholesterolemia: The usual adult dosage of evolocumab is 140 mg once every 2 weeks or 420 mg once every 4 weeks, administered as a subcutaneous injection. Homozygous familial hypercholesterolemia: The usual dosage of evolocumab is 420 mg once every 4 weeks administered as a subcutaneous injection. Evolocumab 420 mg can be administered subcutaneously once every 2 weeks if an adequate response is not achieved.

II. Summary of the Submitted Data and Outline of the Review by Pharmaceuticals and Medical Devices Agency

The submitted data and the review thereof by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below.

1. Origin or history of discovery, use in foreign countries, and other information

Evolocumab (Genetical Recombination) (hereinafter referred to as "evolocumab"), discovered by Amgen Inc. (US), is a recombinant human IgG2 monoclonal antibody against proprotein convertase subtilisin/kexin type 9 (PCSK9), a member of the subtilisin family of serine proteases. This serine protease is expressed mainly in the liver, kidney, and intestine (Zaid A et al. *Hepatology.* 2008;48:646-654). Low-density lipoprotein receptor (LDLR) on the surface of liver cells has a key role for hepatic uptake of low-density lipoprotein cholesterol (LDL-C) from plasma. PCSK9 directly binds to LDLR to form a complex of low-density lipoprotein (LDL), LDLR, and PCSK9. The complex is internalized in liver cells for LDLR degradation, thereby resulting in increased LDL-C levels in the circulating blood (Horton JD et al. *Trends Biochem Sci.* 2007;32:71-77, Brown MS et al. *Science.* 2006;311:1721-1723). Evolocumab binds to PCSK9 to inhibit PCSK9 from binding to LDLR, leading to the inhibition of the degradation of LDLR in liver cells, which in turn results in LDL-C reduction in the circulating blood.

The clinical development program of evolocumab was initiated by Amgen Inc. (US) in 2009, and evolocumab was approved in Europe in July 2015 and in the US in August 2015 for the indication of hypercholesterolemia.

In Japan, the clinical development program of evolocumab was initiated by Amgen Inc. (US) in 2012, and taken over by Amgen Astellas BioPharma K.K. in [redacted]. Based on the results of Japanese and foreign clinical studies, a marketing application has been recently filed by the applicant, with the proposed indication of "hypercholesterolemia, heterozygous familial hypercholesterolemia, and homozygous familial hypercholesterolemia."

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

2.A.(1).1) Preparation and control of cell substrate

Human immunoglobulin (Ig)-producing transgenic mice were immunized with human proprotein convertase subtilisin/kexin type 9 (PCSK9). Hybridoma cell lines were generated by fusing murine myeloma cells with B cells derived from lymph nodes of the transgenic mice. From among these cell lines, the most suitable clone was selected. The gene fragments coding for the variable regions of heavy and light chains of human IgG prepared from this clone and a plasmid containing the constant region of IgG2 were used to generate heavy and light chain expression constructs. The 2 expression constructs obtained were transfected into a Chinese hamster ovary (CHO) cell line in serum-free culture medium, and a cell clone ideal for the manufacture of Evolocumab (Genetical Recombination) (hereinafter referred to as "evolocumab") was selected from among the transfected cell lines obtained. This cell clone was used as the original cells to prepare a master cell bank (MCB) and a working cell bank (WCB).

The MCB, WCB, and cells at the limit of *in vitro* cell age (CAL) were subjected to characterization (isozyme analysis, cDNA base sequence, determination of the copy number, Northern blotting, Southern blotting, amino acid sequence), which confirmed the genetic stability throughout the manufacturing period.

Also, the MCB, WCB, and CAL were subjected to the following purity tests: sterility testing, mycoplasma testing, *in vitro* virus testing, *in vivo* virus testing, transmission electron microscopy, test for mouse antibody production, test for hamster antibody production, retrovirus infectivity test by coculture with mink lung cells, *in vitro* test for bovine viruses, and *in vitro* test for porcine viruses. As a result, neither adventitious viruses nor non-viral adventitious agents were detected within the range of the tests performed.

[redacted]. There is no plan for the preparation of a new MCB, whereas a new WCB will be prepared as necessary.

2.A.(1).2) Manufacturing process

[redacted].

A quality risk management approach was used in the development of the manufacturing process, and the following critical quality attributes (CQAs) were identified. Based on the identification of the processes that affect CQAs and on the detection capability of quality attribute analysis, the strategy for quality control was developed.

- [redacted]

[redacted]

The manufacturing process of the drug substance is validated on a commercial scale.

2.A.(1).3) Safety evaluation of adventitious agents

Except for the CHO cell line as the host cell line, no materials of biological origin are used in the manufacturing process of the drug substance.

A purity test was performed on the MCB, WCB, and CAL [see "2.A.(1).1) Preparation and control of cell substrate"]. Unpurified bulk manufactured on a commercial scale was tested before recovery, for bioburden, adventitious virus, and mycoplasma. The results showed that the bulk was not contaminated by viral or non-viral adventitious agents within the range of the tests performed. Bioburden testing, adventitious virus testing, and mycoplasma testing on the unpurified bulk are set as in-process controls.

A viral clearance test was performed for the purification processes using model viruses. The results showed that the purification processes have an adequate viral clearance capacity (Table 1).

Table 1. Results of viral clearance test

Manufacturing process	Virus reduction factor (log_{10})			
	Xenotropic murine leukemia virus	Pseudorabies virus	Reovirus type 3	Minute virus of mice
[redacted]	[redacted]	[redacted][a]	[redacted][a]	[redacted]
Viral inactivation	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Viral removal by filtration	[redacted][b]	[redacted][b]	[redacted][b]	[redacted]
Total virus reduction factor	≥14.52[b]	≥16.83[b]	≥9.13[b]	≥7.45

a: [redacted]

b: The filtration process for viral removal was tested using minute virus of mice only. The applicant explained that the total viral clearance index, calculated by adding the estimated clearance index for minute virus of mice, was ≥19.65 for xenotropic murine leukemia virus, ≥21.96 for pseudorabies virus, and ≥14.26 for reovirus type 3.

2.A.(1).4) Manufacturing process development (comparability)

The main changes made in the manufacturing process during the drug substance development are described below. The manufacturing processes employed at the Amgen Thousand Oaks (ATO) site were Process 1 (ATO) and Process 2 (ATO), and that employed at the Amgen Rhode Island (ARI) site was Process 2 (ARI), which is the commercial manufacturing process.

- Changes from Process 1 (ATO) to Process 2 (ATO): [redacted]
- Changes from Process 2 (ATO) to Process 2 (ARI): [redacted]

Phase I, phase II, and a part of phase III studies used the drug product manufactured from the drug substance produced by Process 1 (ATO), whereas the main phase III studies used the drug product manufactured from the drug substance produced by Process 2 (ARI) [see "4.(i).*A. Summary of the submitted data*"]. Before the process changes, the comparability of the quality attributes was evaluated. The results confirmed the comparability of the drug substance before and after each process change.

2.A.(1).5) Characterization

(a) Structure

- The primary structure was analyzed by liquid chromatography with tandem mass spectrometry (LC/MS/MS) after reduction, alkylation, and digestion with Lys-C, Asp-N, and trypsin, and by

peptide mapping of tryptic digestion product after reduced alkylation.
- The higher order structure was determined by peptide mapping of non-reduced and reduced Lys-C digestion product, free thiol analysis, Fourier transform infrared spectrophotometry, near-ultraviolet circular dichroism spectroscopy, and differential scanning calorimetry.
- Glycosylation sites and the carbohydrate structures were determined by peptide mapping of peptide-N-glycanase F-treated and untreated samples subjected to tryptic digestion, capillary electrophoresis-sodium dodecyl sulfate (CE-SDS) under reduced conditions, hydrophilic interaction liquid chromatography-mass spectrometry, exhaustive methylation/multi-stage tandem mass spectrometry, and exoglycosidase treatment/mass spectrometry.

(b) Physicochemical properties
- The molecular weight was determined by electrospray ionization time-of-flight mass spectrometry (non-reduced, non-reduced and deglycosylated, reduced, reduced and deglycosylated).
- Charge variants were determined by capillary isoelectric focusing and CEX.
- Size variants were determined by size exclusion high-performance liquid chromatography (SE-HPLC), CE-SDS under reduced and non-reduced conditions, SE-HPLC with static light scattering detector, analytical ultracentrifugation sedimentation velocity, and SE-HPLC under non-reduced and reduced conditions.

(c) Biological properties
- The specificity of evolocumab to PCSK9 was confirmed by competitive enzyme-linked immunosorbent assay (ELISA) using proteins belonging to the subtilisin protease family other than PCSK9 (PCSK1, PCSK2, PCSK4, PCSK7, furin).
- [redacted].
- Evolocumab reversed the PCSK9-induced decrease in the uptake of fluorescence-labeled LDL into HepG2 cells.
- [redacted].

(d) Product-related substances/product-related impurities

Based on the results of analyses described in subsections (a) through (c) above, the following were identified as product-related substances: high-mannose glycans, charge analogs, disulfide bond isomers, fragmented products (low molecular weight species), deglycosylated heavy chains, and glycosylated variants. [redacted].

(e) Process-related impurities

[redacted]. All process-related impurities has been confirmed to be adequately removed during the manufacturing process.

2.A.(1).6 Control of drug substance

[redacted].

2.A.(1).7 Stability of drug substance

Table 2 shows the main stability studies conducted on the drug substance.

Table 2. Summary of main stability studies on drug substance

	Manufacturing process of drug substance	Number of batches	Storage conditions	Study period	Storage configuration

Long-term testing	Process 2 (ARI)	3	−30 ± [redacted] °C	24 months[a]	[redacted]
Accelerated testing		3	5 ± [redacted] °C	6 months	
Stress testing		3	40 ± [redacted] °C	1 months	

a: The stability study is ongoing up to [redacted] months.

Under the long-term storage condition, no clear change in quality attributes was detected throughout the study period.

Under the accelerated condition, high molecular weight species tended to increase.

[redacted].

[redacted].

2.A.(2) Drug product

2.A.(2).1) Description and composition of the drug product and formulation development

The drug product is a solution for injection containing 140 mg of evolocumab per glass syringe (1 mL). Excipients contained in the drug product are L-proline, glacial acetic acid, polysorbate 80, sodium hydroxide, and water for injection.

[redacted]. The pen-type product is a combination product that is presented as a prefilled syringe integrated with an autoinjector pen, and it is packaged in a carton. The autoinjector pen is certified in Japan (Certification No. 227AOBZX00003000).

2.A.(2).2) Manufacturing process

The manufacturing process of the drug products (syringe product and pen-type product) is comprised of the following steps: thawing of the drug substance and preparation of drug solution, pre-filtration and storage, sterile filtration, filling and capping, assembling, labeling, packaging and storage, and testing. [redacted].

The manufacturing process of the drug product is validated on a commercial scale.

2.A.(2).3) Manufacturing process development (comparability)

[redacted]. The comparability of the quality attributes was evaluated, and the results confirmed the comparability of the drug product before and after each process change.

2.A.(2).4) Control of drug product

[redacted].

2.A.(2).5) Stability of drug product

The main stability studies of the drug product are shown in Table 3. The drug product manufactured from the drug substance produced by Process 2 (ARI) was used in the stability studies.

Table 3. Summary of main stability studies of drug product

	Number of batches	Storage conditions	Study period	Storage container
Long-term testing	3	5 ± 3°C	24 months[a]	Glass syringe
	1			Glass syringe loaded in pen-type injector
Accelerated testing	3	25 ± [redacted]°C	6 months	Glass syringe
	3	30 ± [redacted]°C	1 months	
	1	25 ± [redacted]°C	6 months	Glass syringe loaded in pen-type injector
	1	30 ± [redacted]°C	1 months	
Stress testing	3	40 ± [redacted]°C	1 months	Glass syringe
	1			Glass syringe loaded in pen-type injector
Photostability testing	1	Overall illuminance of ≥1.2 million lux·h, integrated near ultraviolet energy of ≥200 W·h/m^2, 5 ± 3°C		Glass syringe (unpackaged, packaged in paper box, or paper box and aluminum foil)
	1	2000 lux, 25°C, 14 days		Glass syringe (unpackaged, or packaged in aluminum foil)
Temperature cycle testing	3	3 cycles at temperatures from −30°C to 25°C, then [redacted]°C for [redacted] months		Glass syringe

a: The stability study is ongoing up to [redacted] months.

Under the long-term storage condition, no clear change in quality attributes was detected throughout the study period.

[redacted].

Under the stress condition, an increase in high molecular weight species was observed, in addition to the same changes as those observed under the accelerated condition.

The photostability testing showed that the drug product is photolabile.

In the temperature cycle testing, no clear change in quality attributes was detected throughout the study period.

Based on the above, a shelf life of 24 months has been proposed for the drug product when stored in a glass syringe protected from light at 2°C to 8°C.

2.A.(3) Reference materials

[redacted].

[redacted].

2.B Outline of the review by PMDA

Based on the submitted data, PMDA has concluded that the quality of the drug substance, the drug product, and the syringe is controlled in an appropriate manner.

3. Non-clinical data

3.(i) Summary of pharmacology studies

3.(i).A Summary of the submitted data

3.(i).A.(1) Primary pharmacodynamics

3.(i).A.(1).1) *In vitro* pharmacology studies

(a) Binding affinity to PCSK9 of different animal species (Attached document 4.2.1.1-1)

The binding affinity of Evolocumab (Genetical Recombination) (hereinafter referred to as "evolocumab") to proprotein convertase subtilisin/kexin type 9 (PCSK9) of humans, cynomolgus monkeys, hamsters, and mice was investigated. The results showed that the equilibrium dissociation constant (K_D) of the binding of evolocumab to PCSK9 of humans, cynomolgus monkeys, hamsters, and mice was approximately 16, 8, 14, and 17,000 pmol/L, respectively.

(b) Inhibition of binding of human PCSK9 to human LDLR (Attached document 4.2.1.1-2)

Human low-density lipoprotein receptor (LDLR) was immobilized onto microtiter wells, and biotinylated wild-type human PCSK9 (WT PCSK9) or the gain-of-function PCSK9 variants (D374Y PCSK9) was added to the wells together with various concentrations of evolocumab to determine the activity of evolocumab to inhibit the binding of WT PCSK9 and D374Y PCSK9 to human LDLR. The 50% inhibitory concentration (IC_{50}) of evolocumab against the binding of WT PCSK9 and D374Y PCSK9 to human LDLR was 1.94 ± 0.32 and 0.25 ± 0.16 nmol/L (mean ± standard deviation [SD]), respectively.

(c) Effect on LDLR protein levels in cultured cells (with or without statins) (Attached document 4.2.1.1-4)

Evolocumab (1, 3, 10 μg/mL) or vehicle (10 mmol/L sodium acetate solution containing 9% sucrose) was added to HepG2 cells. After 48 hours of incubation, total LDLR in cells was measured using anti-LDLR antibodies. Regardless of the concentration of evolocumab added, the LDLR protein levels in cells treated evolocumab were slightly higher than that in cells treated with the vehicle. Similar results were observed when the LDLR protein level on the cell surface was measured by flow cytometry.

Lovastatin (1 μg/mL), which is an HMG-CoA reductase inhibitor (statin), or vehicle was added to HepG2 cells, and the mixture was incubated for 48 hours. Total LDLR protein levels on the cell surface and within cells were higher after addition of lovastatin than after addition of the vehicle. Similarly, lovastatin (1 μg/mL) and evolocumab (1-10 μg/mL) were added to HepG2 cells and the mixtures were incubated. Evolocumab dose-dependently increased the total LDLR protein levels on the cell surface and within cells. Addition of evolocumab in combination with lovastatin further increased the total LDLR protein levels on the cell surface and within cells compared with either of the drugs alone.

(d) Effect on LDL uptake into cells (Attached document 4.2.1.1-3)

Addition of WT PCSK9 or D374Y PCSK9 to HepG2 cells reduced the uptake of fluorescence-labeled LDL into cells. In contrast, when WT PCSK9 or D374Y PCSK9 was incubated with various concentrations of evolocumab and then the mixtures were added to HepG2 cells, the decrease in the uptake of fluorescence-labeled LDL was inhibited. The IC_{50} of evolocumab for inhibition of LDL uptake by WT PCSK9 and D374Y PCSK9 was 129.6 ± 22.3 and 12.7 ± 4.0 nmol/L, respectively.

3.(i).A.(1).2) *In vivo* pharmacology studies

(a) Effect in Golden Syrian hamster (Attached document 4.2.1.1-5)

Evolocumab (3, 10, 30 mg/kg) was administered subcutaneously in a single dose to male Golden Syrian hamsters (33-35 days of age). Animals in the control group received humanized IgG2 monoclonal antibody (30 mg/kg) against keyhole limpet hemocyanin (KLH). Blood and liver samples were collected before dosing as well as at 1, 3, 10, 14, 18, 22, 26, and 30 days after dosing (n = 4-6/group at each sampling point). In the evolocumab groups, cholesterol levels other than high-density lipoprotein cholesterol levels in serum (i.e., non-HDL-C levels) decreased in a generally dose-dependent manner. and The maximum percent reduction in non-HDL-C levels in all the evolocumab groups as compared with the control group ranged from 60% to 70%, which were almost reached 3 days after dosing. The duration of the treatment effect increased in a dose-dependent manner. The levels of low-density lipoprotein cholesterol (LDL-C) in serum decreased rapidly after dosing of evolocumab, reaching the lowest level at 3 to 10 days after dosing, followed by return to baseline within 22 to 30 days after dosing.

Serum evolocumab concentrations reached a peak at 1 to 3 days after dosing, while the maximum LDL-C lowering effect of evolocumab were achieved sometime after attainment of the maximum serum evolocumab level. Serum HDL-C and total cholesterol (TC) were similar to serum non-HDL-C. Liver homogenates from animals in the same treatment group were combined, and the LDLR protein level was measured using anti-LDLR antibodies. On Day 3, LDLR protein levels in liver homogenates of the evolocumab groups were higher than those in the control group, and the maximum ratio of evolocumab to control was ≥2.9. LDLR protein levels returned to the baseline value before Day 10 in the evolocumab 3 mg/kg group and before Day 18 in the 10 mg/kg group, whereas in the 30 mg/kg group, LDLR protein levels continued to increase up to Day 26. The duration of the effect of evolocumab increased in a dose-dependent manner.

(b) Effect in cynomolgus monkeys (Attached document 4.2.1.1-6)
Evolocumab (0.05, 0.2, 0.5 mg/kg) or vehicle was administered subcutaneously in a single dose to male cynomolgus monkeys (3 years and 9 months to 6 years of age) (n = 5). Blood was collected before dosing and at 0.5, 1, 1.5, 2, 3, 4, 5, 7, 11, and 14 days after dosing to determine serum lipid levels. Evolocumab dose-dependently reduced serum LDL-C, showing a significant difference between the ≥0.2 mg/kg groups and the vehicle group. In the evolocumab 0.2 and 0.5 mg/kg groups, the maximum percent reduction in LDL-C was 56% at 2 days after dosing and 72% at 4 days after dosing, respectively. The serum TC were similar to LDL-C. The maximum percent reduction in serum TC was 22% in the 0.2 group, and that in LDL-C was 29% in the 0.5 mg/kg group. Both results were obtained at 3 days after dosing. Evolocumab did not cause any significant change in HDL-C or triglyceride levels.

3.(i).A.(2) Secondary pharmacodynamics
Binding affinity to subtilisin proteases other than PCSK9 (Attached document 3.2.S.3-1[1)])
The binding affinity of evolocumab to proteases of the subtilisin family members other than PCSK9 (PCSK1, PCSK2, PCSK4, PCSK7, furin) was investigated. Evolocumab did not bind to any of the subtilisin proteases other than PCSK9.

3.(i).A.(3) Safety pharmacology
Effect on cardiovascular system, respiratory rate, and neurobehavioral function (Attached document 4.2.1.3-1)
Evolocumab 300 mg/kg or vehicle was administered intravenously in a single dose to male cynomolgus monkeys (4 to 5.7 years of age) (vehicle was administered on Day 1 and evolocumab on Day 3) to evaluate the effect on cardiovascular function, respiratory rate, and neurobehavioral function (n = 4).

Electrocardiogram (ECG), heart rate, blood pressure, and intraperitoneal temperature were measured from 90 minutes before until 24 hours after dosing. ECG after dosing of evolocumab was within the normal range, showing no effect of evolocumab on PR, QRS, or QTc interval, nor was arrhythmia observed. Also, no effect was observed on heart rate, systolic, diastolic, or mean blood pressure, arterial pressure, or intraperitoneal temperature.

The respiratory rate calculated from the respiration-induced change in arterial pressure did not show any change related to treatment with evolocumab.

Neurobehavioral evaluation was performed before and approximately 25 hours after dosing under restrained or unrestrained (within the cage) conditions. No evolocumab-related changes were observed.

3.(i).A.(4) Pharmacodynamic drug interactions
No data were submitted.

3.(i).B Outline of the review by PMDA

3.(i).B.(1) Evolocumab-induced reduction in serum LDL-C
The applicant's explanation on the serum LDL-C lowering effect of evolocumab:
In vitro studies showed that evolocumab have a high binding affinity to PCSK9, thereby inhibiting PCSK9 from binding to LDLR. In cultured cells, evolocumab increased LDLR protein levels, resulting

1) This study was conducted as part of the characterization of evolocumab.

in the increased uptake of LDL into cells. Also, in *in vivo* studies using animal models, evolocumab decreased serum TC and LDL-C. Based on the above, evolocumab is considered to inhibit PCSK9-mediated LDLR degradation within cells, resulting in an increase in the expression level of LDLR and thereby decreasing LDL-C in the circulating blood.

PMDA's view:
The results of *in vitro* and *in vivo* studies have confirmed that evolocumab specifically binds to PCSK9, thereby inhibiting the binding of LDLR to PCSK9, and that, in hamsters and cynomolgus monkeys, evolocumab decreased serum LDL-C level. In light of these findings, evolocumab is expected to be effective in treating hypercholesterolemia in humans.

3.(i).B.(2) Secondary pharmacodynamics of evolocumab
PCSK9 is expressed mainly in the liver, but the enzyme is also detected in tissues such as the small intestine, kidneys, pancreas, and brain (Seidah NG et al. *Proc Natl Acad Sci USA.* 2003;100:928-933, Poirier S et al. *J Neurochem.* 2006;98:838-850, Langhi C et al. *Biochem Biophys Res Commun.* 2009;390:1288-1293). The applicant explained whether the inhibition of PCSK9 by evolocumab and a resultant reduction in blood LDL-C could have any impact on tissues other than the liver. The details of the explanation are presented in the subsections below.

3.(i).B.(2).1) Possible effects of PCSK9 inhibition in tissues other than liver
In most of non-hepatic tissues expressing PCSK9, evolocumab is expected to increase LDLR expression level (Schmidt RJ et al. *Biochem Biophys Res Commun.* 2008;370:634-640) Evolocumab would also increase the uptake of cholesterol into the tissues from the circulating blood. However, nonclinical studies showed no toxicity findings in any of these tissues [see "3.(iii) Summary of toxicology studies"], nor did clinical studies identify any evolocumab-associated safety risk in non-hepatic tissues.

On the other hand, the published literature has reported that the inhibition of PCSK9 does not affect LDLR expression in kidneys and adrenals (Grefhorst A et al. *J Lipid Res.* 2008;49:1303-1311, Luo Y et al. *J Lipid Res.* 2009;50:1581-1588, Seidah NG et al. *PLoS One.* 2012;7:e41865). In adrenals, cholesterol as the precursor for biosynthesis of steroid hormones is provided via HDL. Therefore, the inhibition of PCSK9 by evolocumab leading to LDL-C reduction in the circulating blood is unlikely to affect biosynthesis of steroid hormones (Vergeer M et al. *N Engl J Med.* 2011;364:136-145, Bochem AE et al. *J Lipid Res.* 2013;54:1698-1704). The results of nonclinical studies did not suggest effects on fertility or reproductive parameters or decreased biosynthesis of steroid hormones in hamsters or cynomolgus monkeys (Attached document 4.2.3.5.1-1, 4.2.3.2-4, 4.2.3.5.3-1). Also, the results of clinical studies revealed no adverse effects on the metabolism of steroid hormones (cortisol, adrenocorticotropic hormone, estradiol, follicle-stimulating hormone, luteinizing hormone, testosterone) in patients who achieved the lowering of serum LDL-C levels to <25 mg/dL following the 1-year treatment with evolocumab at clinical dose (alone or in combination with statins and ezetimibe). Based on the above, the applicant considers that the inhibition of PCSK9 by evolocumab is unlikely to affect non-hepatic tissues in humans.

Human brain requires a large amount of cholesterol. Abnormalities in cholesterol homeostasis in the brain are thought to lead to chronic neurodegenerative disorders (Goedeke L et al. *Neurobiol Dis.* 2014;72:48-53), suggesting a potential effect of hypolipidemic drugs on neural functions. However, since evolocumab is an antibody with a high molecular weight which is unlikely to enter the brain, it is not expected to reach the pharmacologically active levels in the brain when administered at the clinical dose. Therefore, the applicant considers that evolocumab is unlikely to decrease brain cholesterol levels by inhibiting PCSK9 in the brain. The results of safety pharmacology studies and toxicology studies did not show any evolocumab-induced neurobehavioral changes or histopathological changes in the brain (Attached document 4.2.1.3-1, 4.2.3.2-4, 4.2.3.4.1-1), nor did clinical studies detect any effect of evolocumab on cognitive function.

3.(i).B.(2).2) Effect of PCSK9 inhibition on risks associated with diabetes mellitus
The concentrations of PCSK9 in the circulating blood in humans have been reported to be positively correlated with several indices for glucose metabolism such as fasting serum glucose levels, insulin levels, and homeostasis model assessment of insulin resistance (HOMA-IR), an index of insulin

sensitivity (Lakoski SG et al. *J Clin Endocrinol Metab.* 2009;94:2537-2543, Baass A et al. *Clin Chem.* 2009;55:1637-1645). Also, plasma PCSK9 levels in humans have been reported to decrease with fasting (i.e., conditions of decreased insulin levels) (Browning JD et al. *J Lipid Res.* 2010;51:3359-3363), and high fructose intake is shown to increase plasma PCSK9 concentrations in humans (Cariou B et al. *Nutrition & Metabolism.* 2013;10:4). It is highly likely that the observed correlation between PCSK9 concentrations and glucose metabolism is attributable to food effects rather than a causal relationship between PCSK9 concentrations and glucose homeostasis. There is a report that the incidence of diabetes mellitus was not increased in the population with a loss-of-function mutation in PCSK9 (Y142X or C679X) (Cohen JC et al. *N Engl J Med*. 2006;354:1264-1272). These findings suggest that the inhibition of PCSK9 by evolocumab does not increase the risk of diabetes mellitus.

The nonclinical studies of evolocumab investigated plasma and urinary glucose levels, clinical signs, and histopathological findings of the pancreas in hamsters and cynomolgus monkeys (Attached document 4.2.3.4.1-1, 4.2.3.2-4). Clinical studies evaluated blood glucose and glycated hemoglobin (HbA1c). No evolocumab-induced change in glucose homeostasis was observed in any of these studies.

Based on the above, the applicant considers that evolocumab is unlikely to increase the risks associated with diabetes mellitus in humans.

3.(i).B.(2).3) Relationship between statin-induced myopathy and PCSK9 inhibition

Muscle symptoms have been reported to occur in <1% of patients treated with statins in Japan (Chang CH et al. *BMJ open.* 2013;3:1-9, Ooba N et al. *PLoS One.* 2014;9:1-8). The relationship between statin-induced myopathy and the inhibition of PCSK9 was investigated in an *in vivo* study. The results showed that depletion of isoprenoid intermediates in the cholesterol biosynthesis pathway is a critical step leading to myopathy and that decreased cholesterol per se is not the cause of myotoxicity (Attached document 4.2.1.2-1). Therefore, PCSK9 inhibition-induced reduction in blood LDL-C levels, a phenomenon unrelated to depletion of isoprenoid intermediates, is not expected to induce myopathy. Myotoxicity for which a causal relationship to evolocumab could not be ruled out was not observed in clinical studies or nonclinical studies. Based on the above, the applicant considers that evolocumab is unlikely to cause myopathy in humans.

PMDA's view:

PCSK9 is expressed not only in the liver but also in other various organs, which suggests that PCSK9 has functions other than the control of blood LDL-C levels. In nonclinical studies of evolocumab conducted so far, no adverse effects were observed in PCSK9-expressing tissues. However, clinical studies should investigate whether evolocumab causes adverse events by inhibiting PCSK9 in non-hepatic tissues. Also, the safety of evolocumab in clinical use should continue to be evaluated in the post-marketing surveillance, etc.

3.(ii) Summary of pharmacokinetic studies

3.(ii).A Summary of the submitted data

Serum evolocumab concentrations were determined by enzyme-linked immunosorbent assay (ELISA) or by electrochemiluminescence (ECL) assay. The lower limit of quantitation was 400 ng/mL in monkeys and 500 ng/mL in hamsters. Anti-evolocumab antibody in serum was measured by ECL assay. The lower limit of detection was 40 ng/mL in monkeys and 20 ng/mL in hamsters.

Pharmacokinetic (PK) parameter values are expressed as mean or mean ± SD unless specified otherwise.

3.(ii).A.(1) Absorption

3.(ii).A.(1).1) Single-dose administration (Attached document 4.2.1.1-6, 4.2.2.2-1)

Table 4 shows PK parameters of evolocumab following a single subcutaneous or intravenous administration to male monkeys. The absolute bioavailability (BA) of evolocumab following the subcutaneous administration (calculated using the area under serum concentration-time curve from time zero to infinity [AUC_{inf}] following a single subcutaneous or intravenous administration of evolocumab at 3 mg/kg) was approximately 82%. Anti-evolocumab antibody was not detected in the serum of any animals tested.

Table 4. PK parameters following a single subcutaneous or intravenous administration of evolocumab to monkeys

Route of administration	Dose (mg/kg)	n	t_{max}[a] (day)	C_{max} (μg/mL)	AUC_{inf} (μg·day/mL)	CL/F[b] (mL/day/kg)	V_z/F [c] (mL/kg)	$t_{1/2, z}$ (day)
s.c.	0.2	4	1.0	1.82 ± 0.494	4.12 ± 1.52	55.2 ± 21.6	64.8 ± 16.2	0.86 ± 0.13
	0.5	5	1.0	7.83 ± 1.43	21.2 ± 5.75	24 ± 4.8	26.4 ± 6.9	0.74 ± 0.10
	3	5	3.0	71.1 ± 7.17	469 ± 60.1	6.5 ± 0.8	19.3 ± 2.2	2.07 ± 0.17
	10	5	3.0	172 ± 13.9	2570 ± 751	4.1 ± 0.9	23.2 ± 5.0	4.13 ± 1.28
	30	5	3.0	833 ± 157	13,500 ± 4010	2.4 ± 0.8	19.9 ± 5.2	5.92 ± 1.47
i.v.	3	4	-	-	573 ± 109	5.4 ± 1.0	25.3 ± 1.7	2.53 ± 0.50

t_{max}, Time to maximum serum concentration; C_{max}, Maximum serum concentration; CL/F, Apparent total body clearance
V_z/F, Apparent volume of distribution; $t_{1/2, z}$, Terminal elimination half-life; -, Not calculated
a: Median
b: CL for intravenous administration
c: V_{ss} (volume of distribution at steady state) for intravenous administration

3.(ii).A.(1).2) Repeat-dose administration (Attached document 4.2.3.2-1 to 4.2.3.2-4, 4.2.3.5.3-1)

As the PK data on repeated subcutaneous administration of evolocumab, toxicokinetics data from repeat-dose toxicity studies were submitted.

Table 5 shows the PK parameters of evolocumab following repeated subcutaneous administration of evolocumab to male and female hamsters once every week for 13 weeks or once every 2 weeks for 104 weeks.

Table 5. PK parameters following repeated subcutaneous administration of evolocumab to hamsters

Treatment duration (weeks)	Dose (mg/kg)	Sex	n[a]	Time point (Week)	t_{max}[b] (day)	C_{max} (μg/mL)	$AUC_{0\text{-last}}$ (μg·day/mL)
13	100	M	3	1	3	590 ± 45.5	3280 ± 333
			3	13	1	1160 ± 41.6	6710 ± 368
		F	3	1	1	279 ± 234	2040[c]
			3	13	1	823 ± 118	4830 ± 717
	300	M	3	1	1	1830 ± 210	10,000 ± 996
			3	13	1	2140 ± 337	11,700 ± 2570
		F	3	1	3	1390 ± 140	7380 ± 1360
			3	13	1	2010 ± 576	10,500 ± 3400
104	10	M	3	5	1	82.4	538
			3	27	3	69.5	517
		F	3	5	1	69.0	360
			3	27	1	50.2	297
	30	M	3	5	1	317	2360
			3	27	3	285	2390
		F	3	5	1	244	1680
			3	27	1	221	1350
	100	M	3	5	1	1110	9170
			3	27	1	1040	7790
		F	3	5	1	851	7040
			3	27	1	927	6500

a: Number of animals per measuring time point in the 104-week repeat-dose study
b: Median
c: n = 2

Table 6 shows PK parameters of evolocumab following 26 weeks of once-weekly repeated subcutaneous administration to male and female monkeys.

Table 6. PK parameters following repeated subcutaneous administration of evolocumab to monkeys

Dose (mg/kg)	Sex	n	Time point (Week)	t_{max}[a] (day)	C_{max} (μg/mL)	$AUC_{0\text{-last}}$ (μg·day/mL)
3	M	6	1	3	39.1 ± 8.19	210 ± 50.4
		5	26	3	122 ± 35.4	779 ± 218
	F	6	1	3	35.8 ± 5.08	168 ± 31.0
		6	26	2	61.4 ± 20.5	353 ± 118
30	M	6	1	5	466 ± 44.6	2550 ± 215
		6	26	2	1990 ± 656	12,000 ± 3020
	F	6	1	3	496 ± 51.2	2830 ± 368
		6	26	3	1670 ± 183	10,500 ± 938
300	M	6	1	3	5380 ± 1340	28,000 ± 3120
		6	26	3	12,700 ± 1740	80,000 ± 11,000
	F	6	1	3	4530 ± 296	25,900 ± 1560
		6	26	2	10,700 ± 1720	64,200 ± 10,900

a: Median

Pregnant monkeys (days 20 to 22 of gestation, n = 18) subcutaneously received repeated doses of evolocumab 50 mg/kg once every 2 weeks until delivery (up to 11 doses in total). The ratio of mean serum evolocumab concentration (offspring/dam) at 14 days after parturition was 3.7, but serum evolocumab concentrations in the offspring decreased below, or close to, the lower limit of detection (400 ng/mL) by the 91st day after birth.

3.(ii).A.(2) Distribution

No distribution study was conducted for submission of this application.

3.(ii).A.(3) Metabolism

No metabolic study was conducted for submission of this application.

3.(ii).A.(4) Excretion

No excretion study was conducted for submission of this application.

3.(ii).A.(5) Pharmacokinetic drug interactions (Attached document 4.2.3.2-5)

Rosuvastatin 5 mg/kg was orally administered alone or in combination with evolocumab (by subcutaneous injection at 10 or 100 mg/kg once every 2 weeks for 3 months) to male and female monkeys. Table 7 shows the PK parameters of evolocumab and rosuvastatin. Evolocumab did not have any clear effect on the PK of rosuvastatin.

Table 7. PK parameters following concomitant use of evolocumab with rosuvastatin

Dose (mg/kg)	Sex	n	Time point (day)	t_{max}[a]	C_{max}[b]	AUC_{0-t}[c]
Evolocumab						
10	M	3	1	3.3	119 ± 16.9	629 ± 92.9
		3	85	1	168 ± 25.5	992 ± 193
	F	3	1	3.3	113 ± 14.0	613 ± 58.8
		3	85	3.3	127 ± 17.1	717 ± 118
100	M	5	1	3.3	994 ± 160	5500 ± 813
		5	85	3.3	1820 ± 427	10,900 ± 2300
	F	5	1	3.3	1130 ± 174	5960 ± 750
		4	85	3.3	1640 ± 405	9630 ± 2050
Rosuvastatin						
-	M	2	1	4	13.4	145
		3	85	4	12.3 ± 8.24	141 ± 95.9
	F	-	1	-	-	-
		3	85	4	12.5 ± 4.93	169 ± 23.5
10	M	2	1	5	13.5	145
		3	85	4	24.9 ± 19.7	192 ± 96.0
	F	3	1	6	14.0 ± 5.02	168 ± 43.9
		3	85	6	10.2 ± 1.32	162 ± 42.1
100	M	4	1	3	24.8 ± 15.1	208 ± 31.8
		5	85	4	15.0 ± 3.57	189 ± 27.8
	F	5	1	4	22.0 ± 11.3	211 ± 106
		5	85	4	16.4 ± 9.91	179 ± 84.4

a: Median (day for evolocumab, hour for rosuvastatin)
b: μg/mL for evolocumab, ng/mL for rosuvastatin
c: μg·day/mL for evolocumab, ng·h/mL for rosuvastatin

3.(ii).B Outline of the review by PMDA

The applicant's explanation on the reasons for not conducting studies on the distribution, metabolism, or excretion of evolocumab:

Evolocumab is an IgG antibody with a high molecular weight (approximately 144,000). In a single intravenous administration study in monkeys, V_{ss} of evolocumab (25.3 mL/kg) was similar to the plasma volume of monkeys (45 mL/kg), suggesting only limited distribution from blood to tissues. The following reports on metabolism and excretion are available: (1) evolocumab, an IgG antibody, is eliminated via specific binding and complex formation with the target molecule PCSK9, as well as neonatal Fc receptor (FcRn)-mediated recycling and removal by the reticuloendothelial system (Waldmann TA et al. *Prog Allergy.* 1969;13:1-110, Junghans RP et al. *Proc Natl Acad Sci USA.* 1996;93:5512-5516), and (2) evolocumab is degraded into peptides and amino acids through catabolism. According to the literature, endogenous IgG (Telemo E et al. *J Mammary Gland Biol Neoplasia.* 1996;1:243-249, Kim K et al. *Acta Paediatr.* 1992;81:113-118) and other IgG antibodies (Vasiliauskas EA et al. *Clin Gastroenterol Hepatol.* 2006;4:1255-1258, Kane S et al. *J Clin Gastroenterol.* 2009;43:613-616) are excreted into milk in humans. The applicant considers that an IgG antibody evolocumab is excreted into milk in a similar manner.

Thus, the available published information allow reasonable prediction of the distribution, metabolism, and excretion of evolocumab. Therefore, no nonclinical studies on the distribution, metabolism, or excretion of evolocumab were conducted for submission of the application for evolocumab.

PMDA's view:

Although nonclinical studies on the distribution, metabolism, or excretion of evolocumab were not conducted, the applicant's explanation that currently available information allows the prediction of the distribution, metabolism, and excretion of evolocumab is acceptable. Also, taking account of the submitted data and the applicant's explanation, the evaluation of nonclinical PKs of evolocumab is shown to be appropriate.

3.(iii) Summary of toxicology studies

3.(iii).A Summary of the submitted data

The following toxicology studies of evolocumab were conducted: repeat-dose toxicity studies, carcinogenicity studies, reproductive and developmental toxicity studies, local tolerance studies, and other toxicity studies (cross-reactivity studies). Evolocumab binds with high affinity to human PCSK9 and it also binds with similar affinity to cynomolgus monkey and hamster PCSK9. For this reason, toxicity studies of evolocumab were conducted using hamsters and cynomolgus monkeys.

3.(iii).A.(1) Single-dose toxicity

No single-dose toxicity studies of evolocumab were conducted. However, neither death nor signs of acute toxicity were observed following a single intravenous dose of evolocumab in cynomolgus monkeys in a safety pharmacology study or after the initial dose in hamsters and cynomolgus monkeys in repeated subcutaneous toxicity studies. Based on the findings, the approximate lethal dose was considered by the applicant to be >300 mg/kg.

3.(iii).A.(2) Repeat-dose toxicity

As repeat-dose toxicity studies of evolocumab, the applicant conducted 28-day and 3-month subcutaneous toxicity studies in hamsters and 6-week and 6-month subcutaneous toxicity studies in cynomolgus monkeys. Also, in order to evaluate the toxicity of evolocumab in combination with rosuvastatin, a 3-month subcutaneous toxicity study was conducted in cynomolgus monkeys. Except for the changes in cholesterol levels induced by the pharmacological action of evolocumab, no significant changes were observed in clinical signs or toxicity findings in any of the studies. In the 3-month subcutaneous toxicity study in hamsters and in the 6-month subcutaneous toxicity study in cynomolgus monkeys, the no observed adverse effect level (NOAEL) was 300 mg/kg/week for both studies and $AUC_{0\text{-last}}$ was 11,100 μg·day/mL and 72,100 μg·day/mL, respectively, which was 46 and 300 times $AUC_{week\ 8\text{-}12}$ (962 μg·day/mL)[2)] in patients with hypercholesterolemia (HC) receiving subcutaneous injection of evolocumab 420 mg once every 4 weeks (Study 20101154) and 21 and 137 times $AUC_{week\ 8\text{-}10}$ (1050 μg·day/mL)[2)] in patients with severe familial hypercholesterolemia receiving subcutaneous injection of evolocumab 420 mg once every 2 weeks (Study 20110271).

3.(iii).A.(2).1) Twenty-eight-day repeated subcutaneous toxicity study in hamsters (Attached document 4.2.3.2-1)

Evolocumab (0 [vehicle (10 mmol/L sodium acetate solution containing 9% sucrose)], 30, 100, 300 mg/kg) was administered subcutaneously once every week for 28 days to male and female Golden Syrian hamsters (n = 30/sex/group). Except for decreased serum LDL-C, TC, and HDL-C in the ≥30 mg/kg groups, there were no deaths or abnormalities in clinical signs, body weight, food consumption, ophthalmological examination, organ weight, necropsy findings, or histopathological findings. In the ≥100 mg/kg groups, decreased LDL-C persisted for approximately 8 weeks after the last dose. Clinical chemistry findings included increased alkaline phosphatase (ALP) in males in the ≥30 mg/kg groups and increases in protein and globulin in males in the 300 mg/kg group, but the changes were mild and reversible. Histopathological examination and laboratory test detected no abnormality. Based on the findings, the applicant considered that the above changes were not toxicologically significant. No immunogenicity was observed. Based on the above, the NOAEL was determined to be 300 mg/kg/week.

3.(iii).A.(2).2) Three-month repeated subcutaneous toxicity study in hamsters (Attached document 4.2.3.2-2)

Evolocumab (0 [vehicle], 100, 300 mg/kg) was administered subcutaneously once every week for 3 months to male and female Golden Syrian hamsters (n = 6/sex/group). Except for decreased serum LDL-C, TC, and HDL-C observed in the ≥100 mg/kg groups, there were no deaths or abnormalities in clinical signs, body weight, food consumption, laboratory test, organ weight, necropsy findings, or histopathological findings. No immunogenicity was observed. Based on the above, the NOAEL was determined to be 300 mg/kg/week.

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2) Adjusted for duration of exposure

3.(iii).A.(2).3) Six-week repeated subcutaneous toxicity study in monkeys (Attached document 4.2.3.2-3)

Evolocumab (0 [vehicle], 3, 30, 300 mg/kg) was administered subcutaneously once every week for 6 weeks to male and female cynomolgus monkeys (n = 5/sex/group). There was no evolocumab-related death or euthanasia. Except for decreased serum LDL-C levels accompanied by decreased PCSK9 concentrations observed in the ≥3 mg/kg groups, there were no abnormalities in clinical signs, body weight, food consumption, ECG, ophthalmological examination, organ weight, necropsy findings, histopathological findings. Increased organ weight accompanied by splenic lymphoid hyperplasia was observed in 1 of 3[3)] males in the 300 mg/kg group. This animal had eosinophilic granuloma in the liver, suggesting a history of parasitic infection. The applicant therefore considered that the finding was not attributable to evolocumab. Anti-evolocumab antibodies were detected in 1 of 3 males in the 300 mg/kg group after the completion of treatment with evolocumab, and in 1 of 3 males in the 30 mg/kg group and 1 of 3 females in the 300 mg/kg group during the withdrawal period. However, because of the low incidence of the antibodies during the treatment period and because of the lack of PK or pharmacodynamic (PD) impact, the applicant considered that the occurrence of anti-evolocumab antibody did not affect the toxicity evaluation. Based on the above, the NOAEL was determined to be 300 mg/kg/week.

3.(iii).A.(2).4) Six-month repeated subcutaneous toxicity study in monkeys (Attached document 4.2.3.2-4)

Evolocumab (0 [vehicle], 3, 30, 300 mg/kg) was administered subcutaneously once every week for 6 months to male and female cynomolgus monkeys (n = 6/sex/group). Except for decreased serum LDL-C levels observed in the ≥3 mg/kg groups, there were no deaths or abnormalities in clinical signs, body weight, food consumption, ECG, hematology findings, ophthalmological examination, organ weight, necropsy findings, or histopathological findings. Neutralizing antibodies against evolocumab were detected in 1 of 6 males in the 3 mg/kg group and in 1 of 6 females in the 30 mg/kg group during the withdrawal period, but because of the low incidence of the antibodies, the applicant considered that the antibodies did not affect the toxicity evaluation of evolocumab. T-cell-dependent antibody response assay showed a decrease, or tendency toward a decrease, in the production of IgG antibody against keyhole limpet hemocyanin (KLH) in the ≥3 mg/kg groups at 7 days after primary immunization with KLH and at 7 days after secondary immunization with KLH, whereas IgM antibody production at 7 days after primary immunization with KLH was not affected. In this study, however, 6 of 12 animals in the control group, 4 of 12 in the 3 mg/kg group, 3 of 12 in the 30 mg/kg group, and 4 of 12 in the 300 mg/kg group had already been positive[4)] for anti-KLH antibodies before primary immunization with KLH. These animals have been reported to be apt to develop stronger IgM and IgG responses after the KLH immunization (Lebrec H et al. *Regul Toxicol Pharmacol*. 2014;69:7-21). Analysis of data excluding these animals revealed no differences in IgM or IgG antibody production among the treatment groups, indicating that evolocumab had no effect on immunoglobulin class switching. Immunophenotyping assay using peripheral blood did not show any effect on white blood cell count, lymphocyte count, or peripheral lymphocyte subsets, indicating that sensitivity to infection or infestation did not increase in animals treated with evolocumab. There were no effects on the weight of lymphatic organs or on the histopathological findings. The applicant therefore considered that evolocumab did not inhibit immune functions. Based on the above, the NOAEL was determined to be 300 mg/kg/week.

3.(iii).A.(2).5) Three-month repeat-dose toxicity study in monkeys with concomitant use of rosuvastatin (Attached document 4.2.3.2-5)

Male and female cynomolgus monkeys (n = 3-5/sex/group) received subcutaneous evolocumab (0 [vehicle], 10, 100 mg/kg) once every 2 weeks for 3 months and repeated oral doses of rosuvastatin (0 [empty gelatin capsule], 5 mg/kg/day). Also, a group of animals receiving rosuvastatin (5 mg/kg/day) alone was included in the study. Evolocumab in combination with rosuvastatin did not show pharmacokinetic drug interactions [see "3.(ii).A.(5) Pharmacokinetic drug interactions"]. The rosuvastatin alone group did not show any effect on clinical chemistry findings, whereas the evolocumab + rosuvastatin group showed marked reductions in serum LDL-C and TC levels compared with the

3) Animals in the recovery group were excluded from the denominator.

4) In experimental colonies of non-human primates, latent infection with Schistosoma mansoni, a parasite which has a common epitope to that of KLH, is frequently observed, resulting in animals positive for anti-KLH antibodies (Geyer H et al, *J Biol Chem*. 2005;280(49):40731-40748).

evolocumab alone group. Decreased triglyceride levels were also noted in females in the evolocumab 100 mg/kg group. All of these changes in laboratory values returned to normal completely during a 4-month withdrawal period. There were no effects on clinical signs, food consumption, body weight, ophthalmological examination, vital signs, laboratory test, organ weight, necropsy findings, or histopathological findings in any of the groups. Also, no effects were observed in peripheral lymphocyte subsets, T-cell-dependent antibody response with anti-KLH antibody (IgM, IgG) as the index, or natural killer cell activity. In addition, no immunological effects were observed in hematology or in histopathological examination of lymphatic tissues. Based on the above, the applicant considered that evolocumab is unlikely to affect the immune system when concomitantly administered with rosuvastatin. Following administration of evolocumab in combination with rosuvastatin (5 mg/kg/day), anti-evolocumab antibodies were detected in 1 of 6 animals in the evolocumab 10 mg/kg group and in 1 of 10 animals in the 100 mg/kg group, and the antibody in the latter animal was neutralizing. However, because of the low incidence of anti-evolocumab antibodies, the applicant considered that the antibodies did not affect the toxicity evaluation in the study. Based on the above, the NOAEL of evolocumab in combination with rosuvastatin (5 mg/kg/day) was determined to be 100 mg/kg/2 weeks.

3.(iii).A.(3) Carcinogenicity

Evolocumab is a recombinant protein that consists of only natural amino acids and does not contain inorganic or organic linkers or any other non-protein moieties. Evolocumab is therefore unlikely to directly interact with DNA or other chromosomal substances and, in consequence, the risk of its genotoxicity is extremely low. A carcinogenicity study was conducted in hamsters in order to evaluate potential carcinogenic risk due to chronic inhibition of PCSK9 and to its pharmacological reactions.

3.(iii).A.(3).1) Carcinogenicity study in hamsters (Attached document 4.2.3.4.1-1)

Evolocumab (0 [vehicle], 10, 30, 100 mg/kg) was administered subcutaneously once every 2 weeks for 105 weeks to male and female Golden Syrian hamsters (n = 60/sex/group). The number of surviving females in the control group decreased to 20 from 60 by Week 86, whereupon the study was terminated prematurely. Evolocumab did not affect the survival of animals. Neoplastic lesions noted in the evolocumab groups more frequently than in the control group were adrenocortical adenocarcinoma, thyroid follicular cell adenoma, Harderian gland adenoma, and uterine epithelial tumor, but the incidences of the changes were within the range of the historical data of carcinogenicity studies in hamsters (McInnes E et al. *Toxicol Pathol*. 2013;41:86-97, Pour P et al. *J Natl Cancer Inst*. 1976;56:949-961). No correlation was observed between the incidence of tumors and exposure to evolocumab or the PD impact. Serum LDL-C levels were 70% to 85% lower in the 100 mg/kg group than in the control group. In the 100 mg/kg group, the exposure to evolocumab ($AUC_{week\ 27\text{-}29}$) was 7170 μg·day/mL, which was 15 times $AUC_{week\ 8\text{-}12}$ (962 μg·day/mL)[2)] in patients with HC receiving subcutaneous evolocumab 420 mg once every 4 weeks. Based on the above, the applicant considered that chronic inhibition of PCSK9 by evolocumab is unlikely to raise concern for carcinogenicity.

3.(iii).A.(4) Reproductive and developmental toxicity

As reproductive and developmental toxicity studies, the applicant conducted a study of fertility and early embryonic development to implantation in hamsters and an enhanced pre- and postnatal development study, including maternal function (ePPND study), in cynomolgus monkeys. The 6-month repeated subcutaneous toxicity study in monkeys evaluated the weight and histopathology of reproductive organs, menstrual cycle (for females), and sperm motility, density, and morphology (for male). The results showed no effects of evolocumab on these parameters. In this study, $AUC_{0\text{-}336h}$ after administration on gestation day 133 was 5600 μg·day/mL, which was 12 times $AUC_{week\ 8\text{-}12}$ (962 μg·day/mL)[2)] in patients with HC receiving subcutaneous evolocumab 420 mg once every 4 weeks (Study 20101154).

3.(iii).A.(4).1) Study of fertility and early embryonic development to implantation in hamsters (Attached document 4.2.3.5.1-1)

Evolocumab (0 [vehicle], 10, 30, 100 mg/kg) was administered subcutaneously once every 2 weeks to male Golden Syrian hamsters for 4 weeks before mating and to female animals from 2 weeks before mating up to implantation (n = 25/sex/group). There were no deaths or effect on clinical signs or body weight. Evolocumab had no effect on copulation, fertility, reproductive organ weight, sperm count, estrous cycle, ovary, uterus, pregnancy rate, or necropsy findings. Based on the above, the NOAEL was determined to be 100 mg/kg/2 weeks for fecundity, fertility, and early embryonic development.

3.(iii).A.(4).2) Enhanced pre- and postnatal development study, including maternal function (ePPND study) in monkeys (Attached document 4.2.3.5.3-1)

Evolocumab (0 [vehicle], 50 mg/kg) was administered subcutaneously to pregnant cynomolgus monkeys once during the period from gestation day 20 to gestation day 22, once on gestation day 35, and once every 2 weeks throughout the gestation period up to delivery (n = 18). After spontaneous delivery, the offspring was lactated by dams throughout the entire period after birth. Evolocumab had no effect on clinical signs, food consumption, body weight, gestation period, pregnancy outcome, or fetal or post-natal outcome (death of fetuses or newborns). Abortion was observed in 17.6% (3 of 17) of animals in the control group and in 27.8% (5 of 18) of animals in the 50 mg/kg group, which was within the range of the historical control data[5)] from the laboratory. In the control group, all abortions occurred in the third trimester, whereas in the 50 mg/kg group, abortion occurred in 2 animals each in the first and the second trimesters and in 1 animal in the third trimester. Death of newborns occurred in 14.3% (2 of 14) of animals in the control group and in 15.4% (2 of 13) of animals in the 50 mg/kg group, but the incidence was within the range of historical control data[6)] from the laboratory. Evolocumab had no effect on body weight gain of newborns, neurobehavioral evaluation, skeletal evaluation, or external and visceral examinations during necropsy at the end of the observation period of the first 6 months after birth. In the 50 mg/kg group, serum LDL-C and TC levels in dams decreased during the treatment period. Serum evolocumab concentrations in newborns at 14 days after birth were approximately 100 μg/mL, which was higher than the exposure level (C_{max}, 88.7 μg/mL) that exhibited the maximum effect on serum LDL-C and total cholesterol levels in monkeys in the 6-month repeated subcutaneous toxicity study. However, the mean serum LDL-C and total cholesterol levels in newborns were only slightly lower than those in the control group. These results suggested that the pharmacological effect of evolocumab in newborns may be smaller than that in mature animals. Evolocumab concentrations decreased below the lower limit of detection by 91 days after parturition in dams and by 180 days after birth in newborns. This suggested the clearance rate of evolocumab may be lower in newborns. Anti-evolocumab antibodies were detected in 3 of 18 dams in the 50 mg/kg group, but affected neither pharmacokinetics nor pharmacological effect. No anti-evolocumab antibodies were detected in newborns. Based on the above, the developmental NOEL for was determined to be 50 mg/kg/2 weeks.

3.(iii).A.(5) Other toxicity studies

3.(iii).A.(5).1) Local tolerance study in hamsters (Attached document 4.2.3.6-1)

A single dose of 1 mL of the evolocumab solution (140 mg/mL) was subcutaneously injected into the left lumbar region of male Golden Syrian hamsters. There were no deaths or effect on clinical signs, body weight, or food consumption. Slight or mild oedema was observed at the administration site but disappeared completely within 48 hours post-dose without leaving any histopathological change. The applicant considered that the oedema was attributable to the injection procedure and that evolocumab has no local irritant effect.

3.(iii).A.(5).2) Local tolerance study in rabbits (Attached document 4.2.3.6-2)

An intravenous dose of 1 mL of the evolocumab solution (74.8 mg/mL) was administered to male New Zealand white rabbits. There were no deaths or effect on clinical signs, body weight, or administration site. The applicant thus considered that intravenous evolocumab has no local irritant effect.

3.(iii).A.(5).3) Cross-reactivity study using human, monkey, and hamster tissues (Attached document 4.2.3.7.7-1, 4.2.3.7.7-2)

Cross-reactivity of evolocumab (5, 20 μg/mL) was investigated using human, cynomolgus monkey, and Golden Syrian hamster normal tissues. Evolocumab was bound to the following normal tissues: striated skeletal muscles, cardiomyocytes, and skin smooth muscle cells from humans; striated skeletal muscles, cardiomyocytes, eyes (iris), and skin smooth muscle cells from cynomolgus monkeys; and striated skeletal muscles, cardiomyocytes, skin, skin smooth muscle cells, and esophagus from hamsters.

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5) The mean incidence in 12 studies from 2008 to 2012 was 23.9% (range, 6.7%-38.9%).

6) The mean incidence in 12 studies from 2008 to 2012 was 11.2% (range, 0%-20%).

3.(iii).B Outline of the review by PMDA

3.(iii).B.(1) Effect of evolocumab-induced changes in cholesterol metabolism on the immune system

PMDA asked the applicant to explain the effect of evolocumab on immune cells and immune responses taking account of the relationship with cholesterol metabolism and to explain possible risks in clinical use of evolocumab.

The applicant's explanation:
The toxicity studies of evolocumab closely investigated the immunotoxicity endpoints, including T-cell-dependent antibody response (TDAR), peripheral lymphocyte phenotypes, natural killer cell function, histopathology of lymphatic tissues, and hematology. In studies in cynomolgus monkeys (evolocumab alone for 6 months or evolocumab plus rosuvastatin for 3 months), the maximum exposure to evolocumab (AUC) was approximately 300 times the human exposure at 420 mg of evolocumab once monthly, but no effect on immune function was observed. Administration of anti-PCSK9 monoclonal antibody other than evolocumab in combination with atorvastatin to cynomolgus monkeys did not affect immune function (Gelzleichter T et al. *Toxicol Sci.* 2014;140(2):470-80). These data are consistent with the results of *in vitro* studies demonstrating that membrane cholesterol is maintained at a sufficientl level required for growth of mitogen-induced human lymphocytes under conditions where endogenous cholesterol synthesis by HMG-CoA reductase is inhibited by lovastatin and, at the same time, the extracellular LDL concentration is reduced to 0.5 mg/dL (Cuthbert J et al. *Proc Natl Acad Sci U S A.* 1984;81:4539-4543, Cuthbert J et al. *J Biol Chem.* 1986;261:3620-3627, Cuthbert J et al. *J Biol Chem.* 1987;262:7808-7818). In addition, although HDL is known to be important for lymphocyte growth (Cuthbert J et al. *J Biol Chem.* 1987;262:7808-7818), evolocumab did not cause any decrease in lipoprotein fractions including HDL, except for LDL-C [see "4.(iii).B.(3) Efficacy"]. These results suggest that a reduction in blood LDL-C resulting from the inhibition of PCSK9 by evolocumab does not affect the proliferative capacity of lymphocytes; the results are also consistent with the findings obtained in nonclinical and clinical studies of evolocumab where evolocumab did not modulate immune function or increase the risk of infection. Based on the above, the applicant considers that evolocumab does not affect the immune system or increase the risk of infection.

PMDA's view:
The currently available nonclinical study data have not provided any consistent findings that indicate any risk of infection, nor have the clinical study data detected events that may pose any risk of infection. Taking account of these, together with the applicant's explanation on the effect of evolocumab on the immune system, the clinical use of evolocumab is unlikely to increase the risk of infection.

3.(iii).B.(2) Risk of LDL-C reduction affecting pregnancy maintenance and fetuses and newborns

PMDA asked the applicant to explain the risk of evolocumab-induced low blood LDL-C affecting the maintenance of pregnancy and fetal development.

The applicant's explanation:
In the ePPND study in cynomolgus monkeys, serum LDL-C levels decreased by approximately 70% in dams treated with evolocumab throughout the entire gestation period compared with the control group, but no effect was observed on the development of embryos/fetuses (or newborns). Abortion occurred in 27.8% (5 of 18) of animals in the evolocumab group during the entire gestation period, but this incidence was below the upper limit of normal for the laboratory (38.9%). In addition, pregnancy continued on gestation day 100 in 14 of 18 animals and 11 newborns survived on Day 7 after birth. These data were almost comparable to the results of statistical analysis for pregnancy outcomes expected in cynomolgus monkeys (Jarvis P et al, *Birth Defects Research (Part B)*. 2010;89:175-187). Moreover, no correlation was observed between abortion or neonatal death and exposure to evolocumab, serum LDL-C or the degree of decrease in serum LDL-C in dams. These results suggest that decreased plasma cholesterol levels in dams are unlikely to affect the maintenance of pregnancy.

Decreased serum LDL-C levels were also observed in the control group in the ePPND study using cynomolgus monkeys. This finding is consistent with the report on pregnancy-related changes in the homeostasis of cholesterol in non-human primates (Koritnik D et al. *Metabolism*. 1984;33(9):840-844,

Adams M et al. *Arteriosclerosis*. 1987;7:378-384, Yoshida T et al. *Jikken Dobutsu*. 1988;37:257-262). In humans, plasma cholesterol concentrations, including LDL-C, is reported to increase in the second and third trimesters (Bartels A et al. *Obstetric Medicine.* 2011;4:147-151). Although the physiological mechanism of increased cholesterol levels remains unknown, increased sex steroid hormone production is inferred to contribute partly to the mechanism (Chiang A et al. *Life Sci*. 1995;56:2367-2375). Increased levels of progesterone and estradiol were observed in pregnant monkeys as well (Adams M et al. *Arteriosclerosis*. 1987;7:378-384).

A survey of approximately 10,000 pregnant women showed that both decreased and increased cholesterol levels in the maternal body were correlated with an increased risk of preterm delivery, and also strongly suggested the relationship between decreased cholesterol levels in the maternal body and low birth weight in full-term newborns. However, the survey also reported that the decreased cholesterol did not adversely affect the development of embryos, fetuses, or newborns (Connor W et al. *Am J Clin Nutr*. 1978;31:1131-1142, Edison R et al. *Pediatrics*. 2007;120:723-733, McMurry M et al. *Metabolism*. 1981;30:869-879). On the other hand, multiple studies in humans suggest the possibility that hypercholesterolemia in the mother adversely affect the fetal development and pregnancy outcome (Catov J et al. *Am J Obstet Gynecol*. 2007;197:610.e1-7, Gonzalez-Clemente J et al. *Diabetes Metab*. 2007;33:25-29, Khoury J et al. *Am J Obstet Gynecol*. 2005;193:1292-301, Khoury J et al. *Am J Obstet Gynecol.* 2007;196:549.e1-7). There is no consistent tendency in the regulation of cholesterol homeostasis in the maternal body and the increase in the risk of preterm delivery does not show any clear pattern dependent on cholesterol levels. The above findings support the view that fetal development in mammals does not depend on the conditions of cholesterol in the maternal body (Dietschy J et al. *J Lipid Res*. 1993;34:1637-1659).

Publications have reported that cholesterol and related lipoproteins in the brain are all locally synthesized during the early developmental stage (Dietschy J et al. *J Lipids Res*. 2004;45:1375-1397, Wang H et al. *Trends in Endocrinol Metabol*. 2014;25:8-14). It is also reported that the conceptus does not obtain necessary cholesterol from the mother's blood; instead, it synthesizes ≥80% of the amount needed by itself (Woollett L. *Am J Clin Nutr*. 2005;82:1155-1161, Bartels A et al. *Obstetric Medicine.* 2011;4:147-151). Evolocumab does not inhibit cholesterol synthesis; instead, it decreases blood cholesterol levels by promoting the recycling of LDLR mainly in the liver. For these reasons, evolocumab-induced reduction in blood cholesterol levels does not significantly affect the maintenance of cholesterol homeostasis in the brain during the developmental process of fetuses.

The ePPND study showed that newborns were also exposed to evolocumab, but there were no differences in serum LDL-C levels between the evolocumab group and the control group. This may be related to the lower PCSK9 levels in newborns than in the maternal body (Peticca P et al. *ISRN Endocrinology*. 2013;341632), which may have precluded evolocumab from exhibiting its pharmacological effect in newborns, resulting in no between-group difference. These results suggest the difference in the homeostasis of cholesterol between newborns and adults. In fact, serum LDL-C levels are relatively low immediately after birth and tend to increase during the lactation period (ePPND study [see "3.(iii).A.(4).2) Enhanced pre- and postnatal development study, including maternal function (ePPND study) in monkeys"], Dietschy JM et al. *J Lipid Res.* 2004;45:1375-1397). In the ePPND study, there were no changes in the development of newborns or no effect on the neurobehavioral evaluation performed at 1 and 2 weeks after birth. In PCSK9 knockout mice generated in multiple institutions, decreased serum LDL-C levels were observed but no effect on reproduction was shown. Also, there is no report of adverse effects on the behavior or on the development of the central nervous system (Rashid S et al. *Proc Natl Acad Sci USA.* 2005;102:5374-5379, Rousselet E et al. *J Lipid Res.* 2011;52:1383-1391, Parker RA et al. *J Lipid Res.* 2013;54:2400-2409).

Although decreased serum LDL-C levels may increase the risk of preterm delivery, the results of the ePPND study did not show any such effect. The applicant therefore considers that the pharmacological action of evolocumab is unlikely to adversely affect embryofetal development, newborn development, or maintenance of pregnancy.

PMDA's view:
The applicant explained that evolocumab does not have any specific toxic effect on the maintenance of pregnancy or on fetal development. The explanation is acceptable at present, but the possibility that evolocumab increases the risk of preterm delivery cannot be excluded. Therefore, treatment with evolocumab in pregnant women should be considered only if the expected therapeutic benefit outweighs the possible risks associated with the treatment.

The submitted data and the applicant's discussion raise no other particular toxicological concerns.

4. Clinical data

4.(i) Summary of biopharmaceutic studies and associated analytical methods

4.(i).A Summary of the submitted data

During the development process, the manufacturing process for the drug substances was changed [see "2.A.(1).4) Manufacturing process development (comparability)"]. The drug substance manufactured by different processes was used in the clinical studies submitted in this application. The drug substance manufactured by Process 1 was used in all phase I and phase II studies and a phase III study (Study 20110109), and the drug substance manufactured by Processes 1 and 2 was used in Study 20110233 and Study 20110271. In other phase III studies, the drug substance manufactured by Process 2 was used. The formulation used in clinical studies was presented in a vial, an automated mini-doser device (AMD formulation), an autoinjector/pen (AI/pen formulation), or a prefilled syringe (PFS formulation). In Study 20110233 and Study 20110271, the vial formulation was used initially but switched to the AI/pen formulation. The AI/pen formulation was used in all other phase III studies. In Study 20120138 and Study 20120356 (foreign home-use studies using the AI/pen and AMD formulations), the AMD formulation was used in addition to the AI/pen formulation, while in Study 20120348 (a foreign home-use study using the AI/pen and PFS formulations), the PFS formulation was used in addition to the AI/pen formulation. The proposed drug products are the AI/pen and PFS formulations, both of which were produced using the drug substance manufactured by Process 2.

The concentrations of Evolocumab (Genetical Recombination) (hereinafter referred to as "evolocumab") in human serum were measured by enzyme-linked immunosorbent assay (ELISA), and the lower limit of quantitation was 0.8 μg/mL.

Anti-evolocumab antibody levels in human serum were measured by electrochemiluminescence immunoassay. The lower limit of detection was 160 ng/mL. Samples positive for anti-evolocumab antibodies were subjected to receptor binding assay to search for the presence of neutralizing antibodies.

4.(i).A.(1) Bioequivalence between AMD and AI/pen formulations (Study 20110168, Attached document 5.3.1.2-1)

An open-label, randomized, parallel-group, comparative study was conducted in 292 healthy non-Japanese adults to investigate the effect of the formulation on the PK of evolocumab following a single dose of evolocumab 420 mg SC using AMD or AI/pen formulation.

The geometric least-squares mean ratios [90% confidence interval (CI)] of the maximum serum evolocumab concentration (C_{max}) and the area under serum drug concentration-time curve from time zero to the time of the last quantifiable concentration ($AUC_{0\text{-last}}$) of the AMD formulation to those of the AI/pen formulation were 1.10 [1.03-1.18] and 1.06 [0.97-1.14], respectively.

As regards PD, the geometric least-squares mean ratio [90% CI] of the area under the effect curve from Day 1 to Day 85 ($AUEC_{day\ 1\text{-}85}$) of serum low-density lipoprotein cholesterol (LDL-C) (measured by direct method after ultracentrifugation) of the AMD formulation to that of the AI/pen formulation was 1.00 [0.96-1.04]. Time-course changes in serum LDL-C levels and in proprotein convertase subtilisin/kexin type 9 (PCSK9) concentrations following administration of evolocumab were similar in the two formulations.

4.(i).A.(2) Bioequivalence between PFS and AI/pen formulations (Study 20120133, Attached document 5.3.1.2-2)

A two-treatment, two-period crossover, comparative study was conducted in 96 healthy non-Japanese adults to investigate the effect of the formulation on the PK of evolocumab following a single dose of evolocumab 140 mg SC using the PFS or AI/pen formulation (treatment periods separated by a washout period of 56 days).

The geometric least-squares mean ratios [90% CI] of C_{max} and $AUC_{0\text{-last}}$ of the PFS formulation to those of the AI/pen formulation was 1.02 [0.98-1.07] and 1.01 [0.95-1.08], respectively.

As regards PD, the geometric least-squares mean ratio [90% CI] of $AUEC_{day\ 1\text{-}56}$ of serum LDL-C (measured by direct method after ultracentrifugation) of the PFS formulation to that of the AI/pen formulation was 1.00 [0.97-1.03]. Time-course changes in serum LDL-C levels and in PCSK9 concentrations following administration of evolocumab were similar between the two formulations.

4.(i).B Outline of the review by PMDA

PMDA's view:

Only the AI/pen formulation was used and the PFS formulation was not in the Japanese phase III study (Study 20120122) which evaluated the efficacy and safety of evolocumab, although the two formulations have been proposed. However, Study 20120133 demonstrated the bioequivalence of these formulations in terms of serum evolocumab concentrations. In addition, PD profiles (reduction in serum LDL-C and PCSK9 concentrations) of both formulations were shown to be similar. Therefore, the efficacy and safety of evolocumab demonstrated in the Japanese phase III study using the AI/pen formulation are also expected with the PFS formulation.

4.(ii) Summary of clinical pharmacology studies

4.(ii).A Summary of the submitted data

PK parameter values are expressed as mean or mean ± SD unless specified otherwise.

4.(ii).A.(1) Studies in healthy adults

4.(ii).A.(1).1) Single subcutaneous dose study in Japanese and Caucasian subjects (Study 20110121, Attached document 5.3.4.1-2)

Evolocumab (70, 210, 420 mg) was administered subcutaneously in a single dose to 32 healthy Japanese and Caucasian adults. Table 8 shows the PK parameters of evolocumab observed.

Table 8. PK parameters following a single subcutaneous administration of evolocumab

	Dose (mg)	n	t_{max}[a] (day)	C_{max} (μg/mL)	$AUC_{0\text{-last}}$ (μg·day/mL)
Japanese	70	6	3.0	9.53 ± 6.37	76.3 ± 58.0
	210	6	6.5	31.9 ± 11.1	501 ± 218
	420	6	6.5	104 ± 31.4	1970 ± 749
Caucasian	210	6	6.0	33.0 ± 7.06	504 ± 139

a: Median

The analysis of PK parameters in Japanese subjects receiving a single subcutaneous dose of evolocumab revealed that the maximum mean percent reduction in serum LDL-C in the evolocumab 70, 210, and 420 mg groups compared with the placebo group was 40.7%, 60.3%, and 57.6%, respectively. Following a single subcutaneous administration of evolocumab 210 mg, the time-course percent changes from baseline in serum LDL-C and PCSK9 concentrations were similar between Japanese and Caucasian subjects, the maximum mean percent reduction in serum LDL-C compared with the placebo group was 60.3% in Japanese subjects and 66.3% in Caucasian subjects, and the maximum mean percent reduction in serum PCSK9 concentrations compared with the placebo group was 96.2% in Japanese subjects and 96.0% in Caucasian subjects.

Anti-evolocumab antibody levels were measured in 24 subjects in the evolocumab groups and in 8 subjects in the placebo group. The antibodies were detected only in 1 Japanese subject in the 70 mg group, but no neutralizing antibodies were detected in this subject.

4.(ii).A.(1).2) Single subcutaneous and intravenous administration study in non-Japanese subjects (Study 20080397, Attached document 5.3.4.1-1)

A single dose of evolocumab was administered subcutaneously (7, 21, 70, 210, 420 mg) or intravenously (21, 420 mg) to 56 healthy non-Japanese adults. Table 9 shows the PK parameters of evolocumab observed. Serum evolocumab concentrations following subcutaneous dose of 7 mg were below the lower limit of quantitation in all subjects studied.

Table 9. PK parameters following a single dose of evolocumab

Route of administration	Dose (mg)	n	t_{max}[a] (day)	C_{max} (μg/mL)	AUC_{0-t} (μg·day/mL)	V_{ss} (mL)	CL/F[b] (mL/day)
s.c.	21	6	2.0	0.526 ± 0.590	0.771 ± 1.06	-	-
	70	6	4.0	7.19 ± 3.54	48.1 ± 29.9	-	2420 ± 3100
	210	6	5.5	24.7 ± 4.27	343 ± 94.1	-	636 ± 165
	420	6	7.0	46.0 ± 17.2	842 ± 333	-	581 ± 300
i.v.	21	6	-	6.11 ± 0.864	10.7 ± 3.28	3340 ± 558	1640 ± 384
	420	6	-	139 ± 16.0	1550 ± 348	3340 ± 460	278 ± 54.2

-, Not calculated; t_{max}, Time to maximum serum concentration; V_{ss}, Volume of distribution at steady state
CL/F, Apparent total body clearance
a, Median
b, CL in intravenous administration

The evolocumab-induced reductions in serum LDL-C and PCSK9 concentrations tended to increase in a dose-dependent manner. In the group of subjects receiving a single subcutaneous administration of evolocumab 420 mg, serum LDL-C decreased to the lowest level (48.00 ± 13.90 mg/dL) at 22 days after dosing, then increased to a level close to baseline (143.33 ± 18.90 mg/dL) by 71 days after dosing. In the subcutaneous evolocumab 210 mg and 420 mg groups, serum PCSK9 concentrations decreased below the lower limit of quantitation (15 ng/mL) within several hours after dosing, remained below the lower limit of quantitation until 11 days after dosing, and then increased close to baseline.

Anti-evolocumab antibody levels were measured in 42 subjects in the evolocumab groups and in 14 subjects in the placebo group. The antibodies were detected only in 1 subject in the placebo group, and no neutralizing antibodies was detected in this subject.

4.(ii).A.(2) Studies in patients

4.(ii).A.(2).1) Phase II study in Japanese patients with hypercholesterolemia at high cardiovascular risk (Study 20110231, Attached document 5.3.5A.1-10)

Evolocumab was administered subcutaneously to 310 Japanese patients with hypercholesterolemia (HC) at 70 or 140 mg once every 2 weeks (Q2W) or at 280 or 420 mg once every 4 weeks (Q4W) in combination with a statin, namely HMG-CoA reductase inhibitor, (atorvastatin calcium [atorvastatin], fluvastatin sodium [fluvastatin], pitavastatin calcium hydrate [pitavastatin], pravastatin sodium [pravastatin], rosuvastatin calcium [rosuvastatin], or simvastatin). Table 10 shows the PK parameters of evolocumab observed.

Table 10. PK parameters following multiple subcutaneous administration of evolocumab

Dosing interval	Dose (mg)	n	t_{max}[a] (day)	C_{max} (μg/mL)	$AUC_{week\ 8-12}$ (μg·day/mL)
Q2W	70	14	19	7.25 ± 2.95	112 ± 55.5
	140	21	7	26.3 ± 12.6	490 ± 277
Q4W	280	27	7	35.8 ± 17.0	514 ± 291
	420	20	7	68.8 ± 27.0	1140 ± 544

a: Median

Serum LDL-C and PCSK9 concentrations were measured at Weeks 8, 9, 10, 11, and 12. In all groups, serum PCSK9 concentrations remained below the baseline levels (378-418 ng/mL) up to Week 12. $AUEC_{week\ 8\text{-}12}$ of PCSK9 was 7670 ± 2710 and 8840 ± 2630 ng·day/mL in the 70 mg Q2W and 140 mg Q2W groups, respectively, and 8050 ± 2620 and 9060 ± 2960 ng·day/mL in the 280 mg Q4W and 420 mg Q4W groups, respectively. $AUEC_{week\ 8\text{-}12}$ of LDL-C was 2600 ± 532 and 3040 ± 513 mg·day/dL in the 70 mg Q2W and 140 mg Q2W groups, respectively, and 2730 ± 609 and 3030 ± 449 mg·day/dL in the 280 mg Q4W and 420 mg Q4W groups, respectively. The evolocumab-induced reductions in serum LDL-C and PCSK9 concentrations increased in a generally dose-dependent manner both in the Q2W and Q4W groups, and the lowering effect in the 140 mg Q2W regimen group was comparable to that in the 420 mg Q4W regimen group.

Anti-evolocumab antibody levels were measured in 205 patients in the evolocumab group and in 102 patients in the placebo group. The antibodies were detected only in 1 patient in the placebo group, but no neutralizing antibodies were detected in this patient.

4.(ii).A.(2).2) Phase III study in Japanese patients with primary HC and mixed dyslipidemia at high cardiovascular risk (Study 20120122, Attached document 5.3.5A.1-11)

Evolocumab was subcutaneously administered to Japanese patients with primary HC and mixed dyslipidemia (PHMD) at 140 mg Q2W or at 420 mg Q4W in combination with atorvastatin (5 or 20 mg). Table 11 shows the PK parameters of evolocumab observed. When evolocumab was administered by the same dosage regimen, serum evolocumab concentrations at Week 12 were approximately 25% to 50% lower in the evolocumab + atorvastatin 20 mg group than in the evolocumab + atorvastatin 5 mg group.

Table 11. Serum evolocumab concentrations following multiple subcutaneous administration of evolocumab

Evolocumab dosage regimen	Atorvastatin dose (mg)	Serum evolocumab concentration (μg/mL)		
		Week 2	Week 10	Week 12
140 mg Q2W	5	4.32 ± 3.69 (n = 49)	10.5 ± 7.38 (n = 50)	12.0 ± 8.33 (n = 43)
	20	2.20 ± 2.13 (n = 48)	5.83 ± 3.97 (n = 48)	5.80 ± 3.91 (n = 42)
420 mg Q4W	5	29.1 ± 13.0 (n = 47)	35.6 ± 16.4 (n = 44)	13.3 ± 10.0 (n = 49)
	20	28.1 ± 12.8 (n = 48)	34.7 ± 19.7 (n = 42)	9.79 ± 8.31 (n = 49)

The percent reductions from baseline in serum PCSK9 concentrations at Weeks 2, 10, and 12 were 76.55% ± 18.11%, 73.97% ± 17.55%, and 74.19% ± 18.90%, respectively, in the 140 mg Q2W group and 98.15% ± 6.58%, 95.84% ± 9.22%, and 50.76% ± 24.21%, respectively, in the 420 mg Q4W group.

Anti-evolocumab antibody levels were measured in 202 patients in the evolocumab group. The antibodies were detected in 1 patient each in the 140 mg Q2W group and 420 mg Q4W group. In the patient in the 140 mg Q2W group, anti-evolocumab antibodies was detected only at baseline. Neutralizing antibodies were not detected in either of the 2 patients.

4.(ii).A.(2).3) Phase II study in non-Japanese patients with HC (Study 20101154, Attached document 5.3.5A.1-1)

Evolocumab was administered subcutaneously to 411 non-Japanese patients with HC at 70, 105, or 140 mg Q2W or at 280, 350, or 420 mg Q4W. Table 12 shows the PK parameters of evolocumab observed.

Table 12. PK parameters following multiple subcutaneous administration of evolocumab

Dosing interval	Dose (mg)	n	t_{max}[a] (day)	C_{max} (μg/mL)	$AUC_{week\ 8\text{-}12}$ (μg·day/mL)
Q2W	70	15	21	6.40 ± 4.52	89.6 ± 59.3
	105	16	21	14.6 ± 12.2	227 ± 217
	140	21	20	23.7 ± 14.7	387 ± 271
Q4W	280	23	7	43.9 ± 25.7	617 ± 455
	350	23	7	48.4 ± 26.4	704 ± 454
	420	21	7	62.9 ± 24.3	962 ± 459

a, Median

Serum LDL-C and PCSK9 concentrations were measured at Weeks 8, 9, 10, 11, and 12. $AUEC_{week\ 8\text{-}12}$ of serum PCSK9 concentrations was 7160 ± 2910, 8160 ± 3410, and 7740 ± 2930 ng·day/mL in the 70, 105, and 140 mg Q2W groups, respectively, and 6800 ± 2500, 6930 ± 2620, and 8980 ± 3220 ng·day/mL in the 280, 350, and 420 mg Q4W groups, respectively. $AUEC_{week\ 8\text{-}12}$ of serum LDL-C was 1710 ± 690, 2260 ± 488, and 2340 ± 350 mg·day/dL in the 70, 105, and 140 mg Q2W groups, respectively, and 2010 ± 421, 2070 ± 645, and 2460 ± 590 mg·day/dL in the 280, 350, and 420 mg Q4W groups, respectively. The evolocumab-induced reductions in serum PCSK9 concentrations and LDL-C levels increased in a generally dose-dependent manner both in the Q2W and Q4W groups.

Anti-evolocumab antibody levels were measured in 269 patients in the evolocumab groups and in 83 patients in the placebo group. The antibodies were detected in 1 patient each in the evolocumab 105 mg Q2W group and the placebo group, but neutralizing antibodies were not detected in either of the 2 patients.

4.(ii).A.(2).4) Phase I study in non-Japanese patients with HC (Study 20080398, Attached document 5.3.4.2-1)

In combination with a statin, evolocumab was administered subcutaneously to 60 non-Japanese patients with HC according to one of the following dosing regimens: (i) 14 or 35 mg once weekly (QW) for a total of 6 doses, (ii) 140 or 280 mg Q2W for a total of 3 doses, and (iii) 420 mg Q4W for a total of 2 doses. Table 13 shows the PK parameters of evolocumab observed. Serum evolocumab concentrations following multiple subcutaneous administration of evolocumab 14 or 35 mg QW were below the lower limit of quantitation in almost all patients.

Table 13. PK parameters following multiple subcutaneous administration of evolocumab

Dosing interval	Dose (mg)	n	t_{max}[a] (day)	C_{max} (μg/mL)	$AUC_{0\text{-}last}$ (μg·day/mL)
Q2W	140[b]	6	35	20.3 ± 13.2	226 ± 249
	280[b]	6	35	62.8 ± 22.7	1200 ± 634
Q4W	420[b]	6	21	63.6 ± 11.2	903 ± 280
Q2W	140[c]	9	3	16.3 ± 10.8	181 ± 157
	140[d]	4	35	14.7 ± 2.88	165 ± 69.1

a: Median
b: Subjects with HC (non-familial hypercholesterolemia) who were on low- to middle-dose statin therapy (rosuvastatin <40 mg, atorvastatin <80 mg, or simvastatin 20-80 mg)
c: Subjects with HC (non-heterozygous familial hypercholesterolemia) who were on high-dose statin therapy (atorvastatin 80 mg or rosuvastatin 40 mg)
d: Subjects with heterozygous familial hypercholesterolemia

Following subcutaneous administration of evolocumab 140 or 280 mg Q2W or 420 mg Q4W to subjects with HC (non-familial hypercholesterolemia [FH]), serum LDL-C decreased at the first time point (Day 4) after baseline. The decreased LDL-C levels persisted up to Day 78 in the 280 mg Q2W group and up to Day 71 in the 420 mg Q4W group. At the end-of-treatment time point (Day 43 in the Q2W groups, Day 57 in the Q4W group), the percent reduction from baseline in serum LDL-C was 69.58% ± 18.13%, 74.65% ± 3.47%, and 62.01% ± 11.43% in the140 Q2W, 280 mg Q2W, and 420 mg Q4W groups, respectively, and the maximum percent reduction from baseline in serum LDL-C was 77.14% ± 14.14%, 74.65% ± 3.47%, and 77.41% ± 9.40% in the140 Q2W, 280 mg Q2W, and 420 mg Q4W groups, respectively.

Following subcutaneous administration of evolocumab 140 mg Q2W to subjects with heterozygous familial hypercholesterolemia (HeFH), serum LDL-C decreased at the second time point (Day 8) after baseline, and the decreased LDL-C levels persisted up to Day 50.

Anti-evolocumab antibody levels were measured in 43 subjects in the evolocumab groups and in 14 subjects in the placebo group. Anti-evolocumab antibodies were detected only in 1 subject receiving 140 mg Q2W (who was on high-dose statin therapy), but no neutralizing antibodies were detected in this subject.

4.(ii).A.(2).5) Phase II study in non-Japanese patients with HC (Study 20101155, Attached document 5.3.5A.1-2)

Evolocumab was administered subcutaneously to 631 non-Japanese patients with HC at 70, 105, or 140 mg Q2W, or at 280, 350, or 420 mg Q4W, in combination with a statin (atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, or simvastatin). Table 14 shows the PK parameters of evolocumab observed.

Table 14. PK parameters following multiple subcutaneous administration of evolocumab

Dosing interval	Dose (mg)	n	t_{max}[a] (day)	C_{max} (μg/mL)	$AUC_{week\ 8\text{-}12}$ (μg·day/mL)
Q2W	70	10	7	4.52 ± 2.93	67.3 ± 48.8
	105	16	7	9.29 ± 5.30	140 ± 89.5
	140	19	20	17.6 ± 9.31	304 ± 200
Q4W	280	18	7	41.5 ± 16.4	564 ± 245
	350	23	7	40.3 ± 15.5	524 ± 231
	420	21	7	54.6 ± 23.8	746 ± 342

a: Median

The evolocumab-induced reductions in serum LDL-C and PCSK9 concentrations were dose-proportional, with the 140 mg Q2W and 420 mg Q4W groups showing a greater reduction than those in the other regimen groups.

Anti-evolocumab antibody levels were measured in 474 patients in the evolocumab groups and in 155 patients in the placebo group. No anti-evolocumab antibodies were detected in any of the patients.

4.(ii).A.(2).6) Phase II study in non-Japanese patients with HeFH (Study 20090158, Attached document 5.3.5A.1-3)

Evolocumab was administered subcutaneously at 350 or 420 mg Q4W to 168 non-Japanese patients with HeFH. Table 15 shows the PK parameters of evolocumab observed.

Table 15. PK parameters following multiple subcutaneous administration of evolocumab

Dose (mg)	n	t_{max}[a] (day)	C_{max} (μg/mL)	$AUC_{week\ 8\text{-}12}$ (μg·day/mL)
350	17	7	52.1 ± 28.3	723 ± 527
420	16	7	72.4 ± 40.9	1010 ± 653

a: Median

Serum LDL-C and PCSK9 concentrations were measured at Weeks 8, 9, 10, 11, and 12. In both treatment groups, serum PCSK9 concentrations reached their lowest level at 1 week after Week 8 (at the third dose) (5.06 ± 12.3 ng/mL and 2.36 ± 6.46 ng/mL in the 350 and 420 mg groups, respectively), and remained below the baseline level (603 ± 206 and 560 ± 155 ng/mL, respectively) up to Week 12. The maximum percent reductions from baseline in serum LDL-C were achieved (75.8% ± 13.2% and 87.7% ± 7.70% in the 350 and 420 mg groups, respectively) approximately 2 weeks after Week 8, and the percent reductions at Week 12 were 43.7% ± 23.2% and 68.0% ± 19.8%, respectively.

Anti-evolocumab antibody levels were measured in 108 patients in the evolocumab group and in 56 patients in the placebo group. No anti-evolocumab antibodies were detected in any of the patients.

4.(ii).A.(2).7) Phase II study in non-Japanese patients with HC (Study 20090159, Attached document 5.3.5A.1-4)

Evolocumab was administered subcutaneously to 160 non-Japanese patients with HC according to either of the following dosing regimens: (i) 280, 350, or 420 mg Q4W and (ii) 420 mg Q4W in combination with oral ezetimibe (10 mg once daily). Table 16 shows the PK parameters of evolocumab observed.

Table 16. PK parameters following multiple subcutaneous administration of evolocumab

	Dose (mg)	n	t_{max}[a] (day)	C_{max} (μg/mL)	$AUC_{0\text{-last}}$ (μg·day/mL)
Evolocumab alone	280	9	7	42.3 ± 22.9	632 ± 373
	350	10	7	54.4 ± 31.3	893 ± 708
	420	7	7	68.4 ± 24.7	1020 ± 423
Evolocumab + ezetimibe	420	9	7	86.3 ± 37.0	1360 ± 556

a: Median

Serum LDL-C and PCSK9 concentrations were measured at Weeks 8, 9, 10, 11, and 12. In all evolocumab alone groups, serum PCSK9 concentrations reached their lowest level at 1 week after Week 8 (at the third dose) (4.63 ± 9.19 ng/mL in the evolocumab 280 mg alone group, 6.51 ± 9.80 ng/mL in the evolocumab 350 mg alone group, and below the lower limit of quantitation in the evolocumab 420 mg alone group). Serum PCSK9 remained below the baseline level (365-398 ng/mL) up to Week 12. Serum LDL-C concentrations reached their lowest level approximately 1 to 3 weeks after Week 8 (76.3 ± 42.0 in the evolocumab 280 mg alone group, 81.5 ± 41.5 in the evolocumab 350 mg alone group, and 59.7 ± 13.7 ng/mL in the evolocumab 420 mg alone group). $AUEC_{week\ 8\text{-}12}$ of LDL-C was 2670 ± 942, 2900 ± 900, and 3680 ± 669 mg·day/dL, respectively, and evolocumab-induced reduction in serum LDL-C increased in a dose-dependent manner. $AUEC_{week\ 8\text{-}12}$ of LDL-C in the evolocumab 420 mg + ezetimibe group was 3830 ± 745 mg·day/dL, showing a slight increase compared with the evolocumab 420 mg alone group.

Anti-evolocumab antibody levels were measured in 94 patients in the evolocumab groups and in 60 patients in the placebo group. No anti-evolocumab antibodies were detected in any of the patients.

4.(ii).A.(2).8) Phase III study in non-Japanese patients with PHMD (Study 20110115, Attached document 5.3.5A.1-6)

Evolocumab was administered subcutaneously to non-Japanese patients with PHMD at 140 mg Q2W or at 420 mg Q4W in combination with a statin (atorvastatin 10, 80 mg; rosuvastatin 5, 40 mg; simvastatin 40 mg). Table 17 shows serum evolocumab concentrations. When evolocumab was administered by the same dosage regimen, serum evolocumab concentrations at Week 12 were lower in the high-dose atorvastatin and rosuvastatin groups than in the low-dose groups.

Table 17. Serum evolocumab concentrations following multiple subcutaneous administration of evolocumab

Evolocumab dosage regimen	Concomitant drug	Serum evolocumab concentration (μg/mL)		
		Week 2	Week 10	Week 12
140 mg Q2W	Atorvastatin 10 mg	2.21 ± 2.66 (n = 88)	6.01 ± 6.19 (n = 99)	6.63 ± 7.19 (n = 102)
	Atorvastatin 80 mg	1.55 ± 1.93 (n = 84)	4.63 ± 3.93 (n = 97)	5.03 ± 4.48 (n = 99)
	Rosuvastatin 5 mg	1.59 ± 1.92 (n = 85)	5.58 ± 5.71 (n = 95)	6.04 ± 6.56 (n = 100)
	Rosuvastatin 40 mg	1.05 ± 1.77 (n = 82)	3.09 ± 3.41 (n = 92)	2.86 ± 3.21 (n = 96)
	Simvastatin 40 mg	1.82 ± 2.09 (n = 74)	5.85 ± 4.67 (n = 88)	6.20 ± 4.98 (n = 92)
420 mg Q4W	Atorvastatin 10 mg	28.8 ± 14.9 (n = 76)	35.0 ± 19.2 (n = 91)	12.4 ± 10.3 (n = 90)
	Atorvastatin 80 mg	23.8 ± 13.6 (n = 77)	27.5 ± 19.1 (n = 90)	8.09 ± 8.54 (n = 93)
	Rosuvastatin 5 mg	27.5 ± 12.3 (n = 78)	33.7 ± 16.5 (n = 95)	10.2 ± 7.60 (n = 100)
	Rosuvastatin 40 mg	22.2 ± 13.6 (n = 80)	27.3 ± 22.5 (n = 89)	6.74 ± 8.15 (n = 90)
	Simvastatin 40 mg	27.4 ± 13.1 (n = 81)	34.3 ± 20.9 (n = 88)	11.3 ± 10.9 (n = 90)

The percent reductions from baseline in serum PCSK9 concentrations at Weeks 2, 10, and 12 were 54.78% ± 57.03%, 47.78% ± 94.62%, and 51.70% ± 33.63%, respectively, in the 140 mg Q2W group, and 91.08% ± 18.90%, 88.36% ± 22.79%, and 23.38% ± 63.83%, respectively, in the 420 mg Q4W group. The percent reduction from baseline in serum LDL-C at Week 12 was 61.80% ± 18.84% in the 140 mg Q2W group and 57.74% ± 22.39% in the 420 mg Q4W group.

Anti-evolocumab antibody levels were measured in 1115 patients in evolocumab groups. The antibodies were detected in 1 patient in the 140 mg Q2W group and in 2 patients in the 420 mg Q4W group, but all were detected only at baseline. No neutralizing antibodies were detected in any of the 3 patients.

4.(ii).A.(2).9) Phase III study in non-Japanese patients with HeFH (Study 20110117, Attached document 5.3.5A.1-8)

Evolocumab was administered subcutaneously to non-Japanese patients with HeFH at 140 mg Q2W or at 420 mg Q4W in combination with a statin (atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, or simvastatin). Serum evolocumab concentrations at Week 12 were 5.57 ± 7.46 μg/mL (n = 101) in the 140 mg Q2W group and 8.50 ± 7.17 μg/mL (n = 105) in the 420 mg Q4W group, and the concentrations remained at a higher level in the 420 mg Q4W group than in the 140 mg Q2W group.

The percent reductions from baseline in serum PCSK9 concentrations at Weeks 2, 10, and 12 were 52.21% ± 24.68%, 49.33% ± 28.01%, and 47.31% ± 29.54%, respectively, in the 140 mg Q2W group and 93.61% ± 10.19%, 90.32% ± 11.59%, and 13.46% ± 42.20%, respectively, in the 420 mg Q4W group. The percent reductions from baseline in serum LDL-C at Weeks 8 and 12 were 60.42% ± 17.19% and 60.77% ± 15.36%, respectively, in the 140 mg Q2W group and 54.70% ± 22.85% and 56.29% ± 21.76%, respectively, in the 420 mg Q4W group.

Anti-evolocumab antibody levels were measured in 220 patients in the evolocumab groups. No anti-evolocumab antibodies were detected in any of the patients.

4.(ii).A.(2).10) Phase II/III study in non-Japanese patients with homozygous FH (Study 20110233, Attached document 5.3.5B.1-1)

Following administration of evolocumab 420 mg SC Q4W to non-Japanese patients with homozygous FH (HoFH), serum evolocumab concentrations (trough level) at Weeks 4, 8, and 12 were 4.73 ± 3.45 μg/mL (n = 31), 8.12 ± 5.93 μg/mL (n = 31), and 10.9 ± 7.02 μg/mL (n = 30), respectively. Serum evolocumab concentrations (peak level) at Weeks 2, 6, and 10 were 21.1 ± 12.0 μg/mL (n = 8), 35.4 ± 20.1 μg/mL (n = 29), and 26.7 ± 12.9 μg/mL (n = 8), respectively.

The percent reduction from baseline in serum PCSK9 concentrations at Week 12 was greater in the evolocumab group (26.64% ± 30.48%) than in the placebo group (10.88% ± 31.10%).

Anti-evolocumab antibody levels were measured in 41 patients in the evolocumab group and in 16 patients in the placebo group. Anti-evolocumab antibodies were detected in 1 patient in the evolocumab group only at baseline, but no neutralizing antibodies were detected in the patient.

4.(ii).A.(2).11) Long-term extension study in patients with HoFH or severe FH (Study 20110271, Attached document 5.3.5B.2-1)

Patients with HoFH or severe FH[7)] who had not been on low-density lipoprotein (LDL)- or plasma-apheresis at enrollment or within 8 weeks before enrollment in the study (non-apheresis patients) received subcutaneously evolocumab 420 mg Q4W, and patients with HoFH or severe FH who had been on apheresis at enrollment in the study (apheresis patients) received subcutaneously evolocumab 420 mg Q2W. Table 18 shows serum evolocumab concentrations observed. Serum evolocumab concentrations in patients with HoFH or severe FH (on apheresis) receiving evolocumab 420 mg SC Q2W were approximately 15% to 30% lower immediately after apheresis than that before apheresis.

Following administration of evolocumab 420 mg SC Q2W to apheresis patients with HoFH, serum evolocumab concentrations reached their highest level (101 ± 30.6 μg/mL) at approximately 1 week after Week 8 (at the fifth dose), and $AUC_{week\ 8\text{-}10}$ was 1050 ± 359 μg·day/mL.

Table 18. Serum evolocumab concentration following multiple subcutaneous administration of evolocumab (μg/mL)

	Non-apheresis patients (420 mg Q4W)		Apheresis patients (420 mg Q2W)[a]	
	Patients with HoFH	Patients with severe FH	Patients with HoFH	Patients with severe FH
Week 2	38.6 (n = 1)	27.3 ± 14.1 (n = 23)	32.9 ± 15.9 (n = 30)	17.0 ± 10.5 (n = 11)
Week 4	8.42 ± 6.73 (n = 47)	4.62 ± 5.16 (n = 114)	51.9 ± 24.6 (n = 30)	25.8 ± 15.4 (n = 14)
Week 6	34.4 ± 19.6 (n = 45)	29.5 ± 19.9 (n = 101)	61.8 ± 23.6 (n = 32)	39.4 ± 19.9 (n = 13)
Week 8	11.6 ± 10.4 (n = 54)	7.14 ± 7.91 (n = 119)	68.5 ± 26.7 (n = 34)	46.7 ± 24.2 (n = 13)
Week 10	44.6 ± 19.3 (n = 4)	36.8 ± 21.1 (n = 20)	68.3 ± 24.9 (n = 33)	59.4 ± 37.5 (n = 9)
Week 12	12.3 ± 10.6 (n = 66)	10.7 ± 11.2 (n = 108)	77.8 ± 29.0 (n = 29)	65.9 ± 41.2 (n = 5)

a: Value before apheresis

Serum PCSK9 concentrations at Weeks 2, 4, 6, 8, 10, and 12 were measured following administration of evolocumab 420 mg SC Q4W to non-apheresis patients with HoFH (baseline serum PCSK9 concentration, 639 ± 198 ng/mL). Serum PCSK9 concentrations were 32.0, 91.7 ± 145, and 31.5 ± 9.36 ng/mL at Weeks 2, 6, and 10 (when the peak concentration of serum evolocumab was reached), respectively, and ranged from 428 to 467 ng/mL at Weeks 4, 8, and 12 (when serum evolocumab concentration was at the trough level). Following administration of evolocumab 420 mg SC Q2W to apheresis patients with HoFH (baseline serum PCSK9 concentration, 746 ± 214 ng/mL), serum PCSK9 concentrations ranged from 37.4 to 47.6 ng/mL (before apheresis) at Weeks 2, 4, 6, 8, 10, and 12 (when the trough concentration of serum evolocumab was reached).

Anti-evolocumab antibodies were positive in 3 patients. Of these patients, 2 were positive for the antibodies only at baseline. No neutralizing antibodies were detected in any of these 3 patients.

4.(ii).A.(3) Population analysis

4.(ii).A.(3).1) Population pharmacokinetic analysis (Attached document 5.3.3.5-1, 5.3.3.5-2, 5.3.3.5-3)

A population pharmacokinetic analysis (PPK) was performed using serum evolocumab concentration data obtained from 3414 subjects at 16,179 time points in a foreign phase I study in healthy adults (Study 20080397), a foreign phase I study in patients with HC (Study 20080398), foreign phase II studies (Studies 20101155, 20101154, 20090158, and 20090159), and foreign phase III studies (Studies 20110115, 20110114, 20110117, 20110116, and 20110109). The PPK model was constructed in 2 steps. In the first step, a preliminary PPK model was constructed using the data from 6 studies consisting of foreign phase I and II studies and, in the second step, the PPK model constructed in the first step was revised using the data from 5 foreign phase III studies. Covariates were explored only in the first step. The PK of evolocumab was described by a one-compartment model with the first-order absorption

7) HoFH was not included.

process, assuming linear and non-linear disappearance from the central compartment. Candidate covariates on PK parameters were body weight, sex, age, race, and renal function for CL and volume of distribution of the central compartment (V); and body weight, sex, age, race, renal function, baseline PCSK9 concentration, use/non-use of concomitant statins, use/non-use of concomitant ezetimibe, and HeFH for non-linear clearance capacity (V_{max}). As significant covariates, body weight was identified for CL, body weight and sex for V, and body weight, use of concomitant statins, use of concomitant ezetimibe, and baseline PCSK9 concentration for V_{max}.

The model constructed by the above PPK analysis was further refined using the data from the phase I study in healthy Japanese adults (Study 20110121) and the Japanese phase II study (Study 20110231) and the Japanese phase III study (Study 20120122) in patients with HC. Race (Japanese subjects) was investigated as a possible additional covariate for CL, V, and V_{max}. As a result, race (Japanese subjects) was identified as a significant covariate for CL and V. In the final PPK model, the population mean parameter value was 0.0909 L/day for CL, 5.09 L for V, and 11.1 nmol/L·day for V_{max}. The inter-individual variability of CL/F, V, and V_{max} was 54.3%, 28.4%, and 29.9%, respectively.

4.(ii).A.(3).2) PPK analysis/pharmacodynamic analysis (Attached document 5.3.3.5-1, 5.3.3.5-3)

A PPK/pharmacodynamic (PD) analysis was performed to investigate the relationship between the $AUC_{week\ 8\text{-}12}$ of evolocumab and serum LDL-C at Weeks 10 and 12, using serum LDL-C data obtained at 3854 time points from 1312 patients with HC evaluated in the foreign phase II studies (Studies 20101155, 20101154, 20090158, and 20090159). The PPK/PD model was described using an E_{max} model. The $AUC_{week\ 8\text{-}12}$ of evolocumab was estimated from the PPK model constructed based on the results of the foreign phase I and II studies and from the plasma evolocumab concentration data obtained from the foreign phase II studies (Studies 20101155, 20101154, 20090158, and 20090159). As significant covariates, use/non-use of concomitant statins, use/non-use of ezetimibe, and HeFH were identified for baseline serum LDL-C levels, and use/non-use of concomitant statins for effect magnitude.[8)]

The above PPK/PD model was refined using the data obtained from Study 20110121 in healthy Japanese adults and Studies 20110231 and 20120122 in patients with HC. The results of the analysis using the refined PPK/PD model suggested that none of covariates identified for the PK or PD parameters of evolocumab (body weight, sex, baseline PCSK9 concentration, use/non-use of concomitant statins, use/non-use of concomitant ezetimibe, HeFH, race [Japanese subjects]) had any clinically significant effect on the reduction in LDL-C levels.

4.(ii).A.(4) Studies of intrinsic factors

4.(ii).A.(4).1) Study in patients with hepatic impairment (Study 20120341, Attached document 5.3.3.3-1)

A single dose of evolocumab 140 mg was administered subcutaneously to non-Japanese subjects with normal hepatic function, non-Japanese subjects with mild hepatic impairment (Child Pugh class A), and non-Japanese subjects with moderate hepatic impairment (Child Pugh class B) (n = 8 per group). The ratio [90% CI] of the least squares mean (mild hepatic impairment/normal hepatic function) and that of the least squares mean (moderate hepatic impairment/normal hepatic function) of C_{max} of evolocumab were 0.785 [0.478-1.291] and 0.660 [0.401-1.084], respectively, and the ratio [90% CI] of the least squares mean (mild hepatic impairment/normal hepatic function) and that of the least squares mean (moderate hepatic impairment/normal hepatic function) of $AUC_{0\text{-}last}$ were 0.608 [0.321-1.153] and 0.532 [0.281-1.009], respectively.

The ratio [90% CI] of the least squares mean (mild hepatic impairment/normal hepatic function) and that of the least squares mean (moderate hepatic impairment/normal hepatic function) of $AUEC_{day\ 1\text{-}57}$ of serum LDL-C were 0.92 [0.82-1.04] and 1.00 [0.88-1.14], respectively. Time-course changes in serum PCSK9 concentrations were similar among the treatment groups.

8) Effect magnitude = $(E_{max} \times AUC_{week\ 8\text{-}12})/([EC_{50} \times REG] + AUC_{week\ 8\text{-}12})$
E_{max}, Maximum pharmacological effect; EC_{50}, $AUC_{week\ 8\text{-}12}$ required to achieve 50% of E_{max}; REG, Effect of dosage regimen

4.(ii).A.(4).2) Study in patients with renal impairment (Study 20140213, Attached document 5.3.3.3-2)

A single dose of evolocumab 140 mg was administered subcutaneously to non-Japanese subjects with normal renal function (estimated glomerular filtration rate [eGFR], ≥90 mL/min/1.73 m^2), non-Japanese subjects with severe renal impairment (eGFR, 15-29 mL/min/1.73 m^2), and non-Japanese patients with end-stage renal failure on dialysis (n = 6 per group). The ratio [90% CI] of the least squares mean (severe renal impairment/normal renal function) and that of the least squares mean (end-stage renal failure/normal renal function) of C_{max} of evolocumab were 0.649 [0.245-1.719] and 0.372 [0.140-0.986], respectively, and the ratio [90% CI] of the least squares mean (severe renal impairment/normal renal function) and that of the least squares mean (end-stage renal failure/normal renal function) of $AUC_{0\text{-last}}$ were 0.628 [0.197-1.997] and 0.333 [0.105-1.060], respectively.

The ratio [90% CI] of the least squares mean (severe renal impairment/normal renal function) and that of the least squares mean (end-stage renal failure/normal renal function) of $AUEC_{day\ 1\text{-}57}$ of serum LDL-C were 0.92 [0.75-1.13] and 1.04 [0.86-1.26], respectively. Time-course changes in serum PCSK9 concentrations were similar among the treatment groups.

4.*(ii).B Outline of the review by PMDA*

4.(ii).B.(1) Difference in pharmacokinetics of evolocumab between Japanese and non-Japanese subjects

The applicant's explanation on the difference in the PK of evolocumab between Japanese and non-Japanese subjects:

In the phase I study (Study 20110121) in both healthy Japanese and non-Japanese adults, the PK parameters following single-dose administration of evolocumab 210 mg SC was similar between Japanese and non-Japanese subjects. In contrast, the comparison of the exposure (C_{max} and $AUC_{0\text{-last}}$ following –single-dose administration of evolocumab 70-420 mg SC) between healthy Japanese adult subjects (Study 20110121) and healthy non-Japanese adult subjects in a foreign phase I study (Study 20080397) revealed that evolocumab exposure was higher in Japanese subjects than in non-Japanese subjects. Also, the comparison of the exposure (C_{max} and $AUC_{week\ 8\text{-}12}$ following administration of evolocumab 70-140 mg SC Q2W or evolocumab 280-420 mg SC Q4W) between Japanese patients with HC in a Japanese phase II study (Study 20110231) and non-Japanese patients with HC in a foreign phase II study (Study 20101155) revealed that evolocumab exposure was higher in Japanese subjects than in non-Japanese subjects. The observed difference in the exposure is considered attributable to the difference in the body weight of subjects between the clinical studies compared, because (1) the body weight was lower in Japanese subjects than in non-Japanese subjects in all the clinical studies used for comparison and (2) the results of PPK analysis identified body weight as a statistically significant covariate for the PK of evolocumab. On the other hand, the PD effects of evolocumab (reduction in serum LDL-C and PCSK9 concentrations) were similar between Japanese and non-Japanese subjects, as demonstrated in Studies 20110121 and 20080397 in healthy adult subjects and in Studies 20110231, 20101155, 20120122, and 20110115 in patients with HC or PHMD. Moreover, the safety profile of evolocumab in the Japanese population in Japanese clinical studies (Studies 20110231 and 20120122) and long-term extension studies (Studies 20110110 and 20120138) was similar to that observed for the entire population in Japanese and foreign clinical studies in patients with PHMD (including studies in patients without concomitant statins) and long-term extension studies (Studies 20110110 and 20120138).

Although the exposure to evolocumab tended to be higher in Japanese subjects than in non-Japanese subjects, the difference is considered attributable to the difference in the body weight of subjects between the studies used for comparison. In addition, the PD and the safety profile of evolocumab were similar between Japanese and non-Japanese subjects. Based on these results, the applicant considers that there is no clinically significant difference in the PK of evolocumab between Japanese and non-Japanese subjects.

PMDA's view:

The applicant explained that there is no clinically significant difference in the PK of evolocumab between Japanese and non-Japanese subjects. The explanation is acceptable, taking account of the submitted data and of the applicant's discussion. From the point of view of PK and PD, it is reasonable

to use the results of foreign clinical studies to explain the efficacy and safety of evolocumab in Japanese subjects.

4.(ii).B.(2) Pharmacokinetics and pharmacodynamics of evolocumab in patients with HC, HeFH, or HoFH

The same dosage regimen (subcutaneous administration of evolocumab 420 mg once every 4 weeks) has been proposed for patients with HC, HeFH, or HoFH. PMDA asked the applicant to explain whether or not the PK and PD of evolocumab are similar among HC, HeFH, and HoFH patients.

The applicant's response:

The PK and PD of evolocumab were compared among PHMD, HeFH, and HoFH patients, based on the results following administration of evolocumab 420 mg SC Q4W to PHMD patients in the foreign phase III study (Study 20110115), HeFH patients in the foreign phase III study (Study 20110117), and HoFH patients in the foreign clinical studies (Studies 20110233 and 20110271). A PK analysis revealed that serum evolocumab concentrations at Week 12 were 9.68 ± 9.20 μg/mL in Study 20110115, 8.50 ± 7.17 μg/mL in Study 20110117, 10.9 ± 7.02 in Study 20110233, and 12.3 ± 10.6 μg/mL in Study 20110271, showing no significant difference among PHMD, HeFH, and HoFH patients. A PD analysis revealed that the percent reductions from baseline in serum PCSK9 concentrations were 88.36% ± 22.79% and 23.38% ± 63.83% at Weeks 10 and 12, respectively, in Study 20110115; 90.32% ± 11.59% and 13.46% ± 42.20% at Weeks 10 and 12, respectively, in Study 20110117; 90.14% ± 11.1% and 26.64% ± 30.5%at Weeks 6 and 12, respectively, in Study 20110233; and 86.46% ± 18.3% and 31.68% ± 32.0% at Weeks 6 and 12, respectively, in Study 20110271, showing no significant difference among PHMD, HeFH, and HoFH patients. The percent reduction from baseline in serum LDL-C at Week 12 was 57.74% ± 22.39% in Study 20110115, 56.29% ± 21.8% in Study 20110117, and 26.07% ± 23.2% in Study 20110233, and 23.10% ± 22.1% in Study 20110271. Similar results were obtained in PHMD and HeFH patients, but there was a difference between HeFH and HoFH patients. The difference is likely to be due to the decreased LDL receptor function in many HoFH patients (Abifadel et al. *Nat Genet.* 2003;34:154-156, Rader et al. *J Clin Invest.* 2003;111:1795-1803).

PMDA's view:

The results of studies suggested the difference in the dose-response relationship of evolocumab between HC or HeFH patients and HoFH patients. Therefore, from the standpoint of clinical pharmacology, use of the same initial dose of evolocumab in HC or HeFH patients and HoFH patients is not justified. The appropriateness of the dosage and administration of evolocumab in HoFH patients will be further reviewed in "4.(iii).B.(4) Dosage and administration," taking account of the efficacy and safety data obtained in clinical studies.

4.(ii).B.(3) Effect of anti-evolocumab antibody on the pharmacokinetics and pharmacodynamics of evolocumab

The applicant's explanation on the effect of anti-evolocumab antibodies on the PK and PD of evolocumab:

In both Japanese and foreign clinical studies, only <1% of subjects tested positive for anti-evolocumab antibodies, and no neutralizing antibodes were detected in any of subjects. At the time points when anti-evolocumab antibody was positive, serum evolocumab and PCSK9 concentrations were within the range of those observed in subjects negative for anti-evolocumab antibody. Based on the above, the applicant considers that the occurrence of anti-evolocumab antibodies is unlikely to have any significant effect on the PK or PD of evolocumab.

PMDA's view:

Data obtained so far do not suggest any effect of anti-evolocumab antibodies on the PK or PD of evolocumab. However, because of the small number of patients positive for anti-evolocumab antibodies in clinical studies, no clear conclusion cannot be drawn on the effect of anti-evolocumab antibodies on the PK or PD of evolocumab. Therefore, post-marketing information on this issue should be collected, and when new findings become available, the information should be provided to healthcare professionals in an appropriate manner.

4.(ii).B.(4) Administration of evolocumab to patients with hepatic or renal impairment

The applicant's explanation on the administration of evolocumab to patients with hepatic or renal impairment:

In the clinical pharmacology study (Study 20120341) in subjects with mild hepatic impairment (Child Pugh class A) or moderate hepatic impairment (Child Pugh class B), the C_{max} and $AUC_{0\text{-last}}$ of evolocumab tended to decrease with increasing severity of hepatic impairment, whereas the PD (reduction in LDL-C and PCSK9 concentrations) and the safety profile of evolocumab in subjects with hepatic impairment were similar to those observed in subjects with normal hepatic function. In the clinical pharmacology study (Study 20140213) in subjects with renal impairment, the mean C_{max} and $AUC_{0\text{-last}}$ of evolocumab decreased by 30% and 24%, respectively, in patients with severe renal impairment (eGFR, 15-29 mL/min/1.73 m^2) compared with subjects with normal renal function (eGFR, ≥90 mL/min/1.73 m^2), and by 45% for both parameters in patients with end-stage renal failure on dialysis, whereas the PD and safety profile of evolocumab in subjects with severe renal impairment and in patients with end-stage renal failure were similar to those in subjects with normal renal function. In addition, a PPK analysis was performed to estimate $AUC_{week\ 8\text{-}12}$ of evolocumab in healthy adult subjects (eGFR, >80 mL/min), patients with mild renal impairment (eGFR, ≥80 mL/min and ≤50 mL/min), and patients with moderate renal impairment (eGFR, ≥30 mL/min and <50 mL/min), who received evolocumab 140 mg SC Q2W or 420 mg SC Q4W during the studies. The result showed no clear relationship between the severity of renal impairment and $AUC_{week\ 8\text{-}12}$. Furthermore, the results of foreign phase II and III studies did not show any clear relationship between the severity of renal impairment and serum evolocumab concentrations at Week 12. The exposure to evolocumab in subjects with mild or moderate hepatic impairment, in subjects with severe renal impairment, and in patients with end-stage renal failure was lower than that in healthy adult subjects, for an unknown reason.

Although the exposure to evolocumab in subjects with mild or moderate hepatic impairment, in subjects with severe renal impairment, and in patients with end-stage renal failure was lower than that in healthy adult subjects as mentioned above, the PD and safety profile of evolocumab in these patients were similar to those in healthy adult subjects and the exposure to evolocumab in patients with mild or moderate renal impairment was similar to that observed in healthy adult subjects. Thus, the applicant considers it unnecessary to adjust the dose of evolocumab in patients with renal impairment and in patients with mild or moderate hepatic impairment. On the other hand, patients with severe hepatic impairment were excluded from clinical studies of evolocumab and, as a result, there is no experience with use of the drug in this patient population. The package insert will include a precautionary statement regarding the use of evolocumab in this patient population.

PMDA's view:

The submitted data and the applicant's discussion do not suggest the necessity for adjusting the dose of evolocumab in patients with renal impairment or in patients with mild to moderate hepatic impairment. In contrast, there is no experience with use of evolocumab in patients with severe hepatic impairment. In addition, it is unclear why the exposure to evolocumab decreased in patients with mild or moderate hepatic impairment. Furthermore, the exposure tended to decrease with increasing severity of hepatic impairment. Taking account of the above, precautions should be included in the package insert.

4.(ii).B.(5) Drug interactions with statins

The applicant's explanation on the drug interactions of evolocumab with statins:

Drug interactions of evolocumab with statins were investigated based on the PK and PD data obtained in the following studies: foreign phase II (Study 20101154) and phase III (Study 20110114) studies, in both of which non-Japanese HC patients received evolocumab alone; and foreign phase II (Study 20101155), Japanese phase III (Study 20120122), and foreign phase III (Study 20110115) studies, in all of which subjects received evolocumab in combination with a statin. The exposure to evolocumab at Week 8 to Week 12 was compared by dosage regimen between Studies 20101154 and 20101155. The C_{max} and AUC of evolocumab in combination with a statin were lower than those of evolocumab alone by 26% and 21%, respectively, with the 140 mg Q2W regimen, and by 13% and 22%, respectively, with the 420 mg Q4W regimen. In Studies 20120122 and 20110115, serum evolocumab concentrations at Week 12 tended to be lower in subjects receiving evolocumab plus a high-dose statin (atorvastatin or rosuvastatin) than in those receiving evolocumab plus a low-dose statin. Statins have been reported to increase serum PCSK9 concentrations in PHMD patients (Awan Z et al. *Clin Chem.* 2012;58:183-189,

Chen F et al. *Biomarkers.* 2011;16:321-333, Mayne J et al. *Lipids Health Dis.* 2008;7:22). This may have contributed to the decrease in the exposure to evolocumab used in combination with statins. The statin-induced increase in PCSK9, the target molecule of evolocumab, may have enhanced the disappearance of evolocumab mediated by the binding to PCSK9. On the other hand, the percent changes from baseline in serum LDL-C and PCSK9 concentrations in subjects receiving evolocumab alone were similar to those in subjects receiving evolocumab in combination with statins. Furthermore, in the Japanese phase II study in Japanese HC patients (Study 20110231), the percent changes from baseline in serum evolocumab, LDL-C, and PCSK9 concentrations at Week 12 were not significantly different among patients receiving different statins (atorvastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin).

Although the exposure to evolocumab tended to decrease when evolocumab was concomitantly administered with statins, the evolocumab-induced reductions in serum LDL-C and PCSK9 concentrations were similar between subjects receiving evolocumab alone and subjects receiving evolocumab in combination with statins. In addition, there was no significant difference in the observed effect among patients receiving different types of concomitant statins. Taking account of the above, the applicant considers it unnecessary to adjust the dose of evolocumab when concomitantly administered with various statins.

PMDA's view:
The concomitant use of evolocumab with statins resulted in pharmacokinetic interactions, leading to decreased exposure to evolocumab. However, decreased evolocumab exposure did not have any clear effect on reduction in serum LDL-C or PCSK9 concentrations, and the extent of the decrease in evolocumab exposure did not differ depending on the type of concomitant statins. For these reasons, adjustment of the evolocumab dose is not necessary regardless of the type of concomitant statins.

4.(iii) Summary of clinical efficacy and safety

4.(iii).A Summary of the submitted data

The applicant submitted evaluation data, namely the results of the following studies: a foreign phase I study in Japanese and Caucasian subjects, Japanese studies in Japanese subjects (a phase II study, a phase III study, 3 long-term extension studies [non-Japanese subjects included]), and foreign studies (6 phase I studies, 4 phase II studies, 1 phase II/III study, 7 phase III studies). Main study results are described below.

4.(iii).A.(1) Phase I study (Study 20110121, Attached document 5.3.4.1.2; Study period, [redacted] to [redacted])

A randomized, double-blind study was conducted at a single center in a foreign country to evaluate the safety, tolerability, and PK of evolocumab. In this study, 24 healthy Japanese adult subjects (6 in each evolocumab group, 2 in each placebo group) received a single subcutaneous dose of evolocumab (70, 210, 420 mg) or placebo and 8 healthy Caucasian adult subjects (6 in the evolocumab group, 2 in the placebo group) received a single subcutaneous dose of evolocumab 210 mg or placebo. The study drug was administered to 32 randomized subjects and all of the subjects were included in the safety analysis set. During the treatment period, study treatment was discontinued in 3 subjects (1 Japanese in the 70 mg group, 1 Japanese in the 420 mg group, and 1 Caucasian in the 210 mg group). The reasons for discontinuation were loss to follow-up (2 subjects [1 Japanese in the 420 mg group and 1 Caucasian in the 210 mg group]) and consent withdrawal (1 subject [Japanese in the 70 mg group]).

In the Japanese cohort, adverse events were reported by 4 subjects in the placebo group (myalgia/rhinolaryngitis, injection site haemorrhage, skin fissures/sinusitis/viral upper respiratory tract infection, tendonitis), 2 subjects in the 70 mg group (inflammation, abnormal faeces), 5 subjects in the 210 mg group (contusion/inflammation/lip injury/petechiae, upper respiratory tract infection, injection site pain/upper respiratory tract infection, folliculitis, gastroenteritis/injection site haematoma), and 4 subjects in the 420 mg group (laryngitis, otitis externa/burns second degree, injection site haemorrhage, abdominal pain). In the Caucasian cohort, adverse events were reported by 2 subjects in the placebo group (upper respiratory tract infection bacterial, headache/upper respiratory tract infection) and 3 subjects in the 210 mg group (blood creatine phosphokinase [CK] increased/viral upper respiratory tract infection, upper respiratory tract infection, headache/injection site haemorrhage). Adverse events for

which a causal relationship to the study drug could not be ruled out were myalgia in the placebo group and abnormal faeces in the 70 mg group in the Japanese cohort; and blood CK increased and headache in the 210 mg group in the Caucasian cohort. Neither serious adverse events nor death was reported.

4.(iii).A.(2) Phase II studies

4.(iii).A.(2).1) Phase II study in Japanese HC patients with high cardiovascular risk (Study 20110231, Attached document 5.3.5A.1-10; Study period, July 2012 to May 2013)

A randomized, double-blind, parallel-group, placebo-controlled study was conducted at 40 centers in Japan to evaluate the efficacy and safety of evolocumab in concomitant use with statins in Japanese HC patients with high cardiovascular risk (target sample size, n = 50 per group [placebo or evolocumab]).

During the screening/placebo run-in period of up to 6 weeks, placebo corresponding to the volume of a Q4W dose (6 mL) was administered subcutaneously and, during the subsequent 12-week treatment period, evolocumab (70 mg Q2W, 140 mg Q2W, 280 mg Q4W, 420 mg Q4W) or placebo (Q2W or Q4W) was administered subcutaneously.

The key inclusion criteria were HC patients aged ≥20 and ≤80 years who were on stable statin therapy for ≥4 weeks before screening and met the following criteria:

- LDL-C ≥115 mg/dL
- Fasting triglycerides (TG) ≤400 mg/dL
- High cardiovascular risk (meeting at least one of the following)
  - History of coronary artery disease
  - Diagnosis of arteriosclerosis obliterans or peripheral arterial disease
  - History of cerebral infarction
  - Diagnosis of HeFH
  - Type 2 diabetes mellitus diagnosed at ≥3 months before randomization
  - Fasting blood glucose >110 mg/dL at ≥3 months before randomization
  - Patients who met ≥3 of the following criteria: (i) men aged ≥45 years or women aged ≥50 years, (ii) history of hypertension or high blood pressure levels at screening (systolic pressure >140 mmHg or diastolic pressure >90 mmHg for at least 3 measurements), (iii) smoking history, (iv) family history of coronary artery disease in a first-degree relative, and (v) high-density lipoprotein cholesterol (HDL-C) <40 mg/dL.

Subjects were assigned to treatment, stratified according to LDL-C levels at screening (<130 mg/dL, ≥130 mg/dL) and to whether they had HeFH or not.

Of 310 randomized subjects (52 in the placebo Q2W group, 51 in the placebo Q4W group, 50 in the 70 mg Q2W group, 52 in the 140 mg Q2W group, 52 in the 280 mg Q4W group, 53 in the 420 mg Q4W group), 307 subjects (52 subjects, 50 subjects, 49 subjects, 52 subjects, 51 subjects, 53 subjects) received the study drug. The remaining 3 subjects (0 subjects, 1 subject, 1 subject, 0 subjects, 1 subject, 0 subjects) did not receive the study drug because of the consent withdrawal (2 subjects) or at the discretion of the physician (1 subject). All of the 307 subjects were included in the safety analysis set and the full analysis set (FAS). The primary efficacy analysis was based on the FAS. During the treatment period, study treatment was discontinued in 9 subjects (0 subjects, 1subject, 3 subjects, 2 subjects, 1 subject, 2 subjects), with the main reason for discontinuation being consent withdrawal in 6 subjects (0 subjects, 1subject, 3 subjects, 1 subject, 0 subjects, 1 subject).

A total of 20 HeFH patients (4 patients, 3 patients, 2 patients, 3 patients, 4 patients, 4 patients) were enrolled in the study.

Table 19 shows the percent change from baseline in LDL-C (ultracentrifugation) at Week 12, the primary efficacy endpoint.

Table 19. Percent change from baseline in LDL-C (ultracentrifugation) at Week 12 (FAS)

	Q2W			Q4W		
	Placebo	70 mg	140 mg	Placebo	280 mg	420 mg
Baseline value (mg/dL)						
Number of subjects	52	49	52	50	51	53
Mean ± SD	144.4 ± 18.1	143.6 ± 20.6	140.7 ± 23.3	141.8 ± 23.4	141.0 ± 21.2	139.7 ± 18.8
Value at Week 12 (mg/dL)						
Number of subjects	50	48	51	49	51	52
Mean ± SD	140.6 ± 20.3	64.5 ± 30.8	40.5 ± 19.8	141.5 ± 28.4	59.6 ± 19.9	51.2 ± 27.8
Change at Week 12 (mg/dL)						
Number of subjects	50	48	51	49	51	52
Mean ± SD	−3.5 ± 17.5	−79.0 ± 29.6	−99.6 ± 26.9	−0.4 ± 23.0	−81.4 ± 21.5	−88.8 ± 25.9
Percent change at Week 12 (%)						
Number of subjects	52	49	52	50	51	53
Mean ± SD	−2.39 ± 12.33	−55.20 ± 19.32	−71.00 ± 13.36	0.36 ± 16.75	−57.70 ± 12.13	−63.54 ± 18.64
Least squares mean ± standard error (SE)[a]	−2.71 ± 2.16	−55.56 ± 2.23	−71.32 ± 2.16	0.05 ± 2.32	−58.10 ± 2.33	−63.89 ± 2.27
Difference from placebo[a]	-			-		
Least squares mean [95% CI]		−52.85 [−58.84, −46.86] $P < 0.001$	−68.61 [−74.51, −62.71] $P < 0.001$		−58.16 [−64.51, −51.81] $P < 0.001$	−63.94 [−70.23, −57.66] $P < 0.001$

a: Analysis of covariance (ANCOVA) with the treatment group as the factor and LDL-C levels at screening (<130 mg/dL, ≥130 mg/dL) as the covariate

Missing values at Week 12 were imputed by the last observation carried forward (LOCF) approach.

For both Q2W and Q4W regimens, data were first compared between the high-dose evolocumab group and the placebo group. If a significant difference was observed, then data were to be compared between the low-dose evolocumab group and the placebo group.

Table 20 shows the percent changes from baseline in total cholesterol (TC), HDL-C, cholesterol other than HDL-C (non-HDL-C), and TG at Week 12 as the secondary efficacy endpoints.

Table 20. Percent changes from baseline in lipid parameters at Week 12 (FAS)

	Q2W			Q4W		
	Placebo	70 mg	140 mg	Placebo	280 mg	420 mg
TC						
Baseline value (mg/dL)	52 225.2 ± 23.1	49 225.2 ± 27.0	52 219.6 ± 27.6	50 222.8 ± 24.5	51 220.4 ± 25.8	53 222.3 ± 22.4
Value at Week 12 (mg/dL)	51 225.4 ± 25.8	47 144.0 ± 34.8	50 118.7 ± 22.8	50 223.6 ± 32.0	51 141.5 ± 28.2	52 135.1 ± 31.0
Percent change at Week 12 (%)	51 0.58 ± 8.80	47 −36.18 ± 13.50	50 −45.59 ± 9.35	50 0.54 ± 11.72	51 −35.81 ± 9.90	52 −39.28 ± 12.59
HDL-C						
Baseline value (mg/dL)	52 53.9 ± 12.8	49 54.7 ± 13.9	52 53.4 ± 11.7	50 54.0 ± 11.5	51 54.9 ± 13.6	53 55.6 ± 13.5
Value at Week 12 (mg/dL)	51 57.6 ± 15.0	47 60.6 ± 15.4	50 61.8 ± 13.6	50 54.0 ± 12.4	51 63.3 ± 14.8	52 62.6 ± 14.8
Percent change at Week 12 (%)	51 7.35 ± 16.45	47 11.74 ± 14.24	50 17.23 ± 16.59	50 0.55 ± 13.64	51 16.80 ± 15.68	52 13.43 ± 17.09
TG						
Baseline value (mg/dL)	52 139.4 ± 51.8	49 140.9 ± 60.1	52 130.3 ± 47.6	50 138.5 ± 51.2	51 125.7 ± 46.1	53 142.3 ± 58.8
Value at Week 12 (mg/dL)	51 142.6 ± 78.8	47 121.7 ± 52.8	50 111.4 ± 51.0	50 148.8 ± 72.7	51 110.7 ± 45.5	52 127.0 ± 63.3
Percent change at Week 12 (%)	51 3.99 ± 42.03	47 −11.94 ± 22.08	50 −13.85 ± 26.05	50 9.52 ± 38.24	51 −7.41 ± 33.96	52 −9.74 ± 22.93
non-HDL-C						
Baseline value (mg/dL)	52 171.3 ± 23.0	49 170.6 ± 27.2	52 166.3 ± 26.2	50 168.7 ± 26.1	51 165.5 ± 24.4	53 166.7 ± 23.5
Value at Week 12 (mg/dL)	51 167.8 ± 28.2	47 83.4 ± 35.0	50 56.9 ± 18.4	50 169.6 ± 32.9	51 78.2 ± 24.0	52 72.5 ± 32.7
Percent change at Week 12 (%)	51 −1.54 ± 11.12	47 −51.64 ± 17.36	50 −65.48 ± 10.37	50 0.77 ± 14.81	51 −52.71 ± 12.21	52 −56.84 ± 17.26

Upper box, number of subjects; lower box, mean ± SD

Safety was analyzed. Adverse events were reported by 34.6% (18 of 52) of subjects in the placebo Q2W group, 42.0% (21 of 50) of subjects in the placebo Q4W group, 49.0% (24 of 49) of subjects in the 70 mg Q2W group, 53.8% (28 of 52) of subjects in the 140 mg Q2W group, 41.2% (21 of 52) of subjects

in the 280 mg Q4W group, and 58.5% (31 of 53) of subjects in the 420 mg Q4W group. Table 21 shows adverse events reported by more than one subject in any group.

Table 21. Adverse events reported by more than one subject in any group (FAS)

	Q2W			Q4W		
	Placebo	70 mg	140 mg	Placebo	280 mg	420 mg
Number of subjects	52	49	52	50	51	53
Nasopharyngitis	11.5 (6)	20.4 (10)	17.3 (9)	12.0 (6)	23.5 (12)	15.1 (8)
Arthralgia	0 (0)	4.1 (2)	3.8 (2)	0 (0)	3.9 (2)	0 (0)
Blood CK increased	0 (0)	2.0 (1)	3.8 (2)	2.0 (1)	3.9 (2)	3.8 (2)
Rash	1.9 (1)	2.0 (1)	3.8 (2)	0 (0)	0 (0)	3.8 (2)
Gastroenteritis	1.9 (1)	2.0 (1)	3.8 (2)	0 (0)	0 (0)	1.9 (1)
Upper respiratory tract inflammation	0 (0)	0 (0)	3.8 (2)	0 (0)	2.0 (1)	1.9 (1)
Myalgia	1.9 (1)	4.1 (2)	1.9 (1)	0 (0)	0 (0)	3.8 (2)
Constipation	3.8 (2)	4.1 (2)	1.9 (1)	0 (0)	0 (0)	0 (0)
Oropharyngeal pain	0 (0)	2.0 (1)	1.9 (1)	4.0 (2)	0 (0)	0 (0)
Abdominal pain upper	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3.8 (2)
Contusion	0 (0)	0 (0)	0 (0)	4.0 (2)	0 (0)	1.9 (1)
Musculoskeletal stiffness	0 (0)	4.1 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Abdominal discomfort	1.9 (1)	0 (0)	0 (0)	4.0 (2)	0 (0)	0 (0)

% (number of subjects)

Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 1.9% (1 of 52) of subjects in the placebo Q2W group, 2.0% (1 of 50) of subjects in the placebo Q4W group, 8.2% (4 of 49) of subjects in the 70 mg Q2W group, 7.7% (4 of 52) of subjects in the 140 mg Q2W group, 3.9% (2 of 51) of subjects in the 280 mg Q4W group, and 9.4% (5 of 53) of subjects in the 420 mg Q4W group. The adverse event for which a causal relationship to the study drug could not be ruled out and which occurred in more than one subject in any group was blood CK increased (2 subjects in the 420 mg Q4W group).

No deaths were reported. Serious adverse events occurred in 1 subject in the 140 mg Q2W group (fracture), 1 subject in the 280 mg Q4W group (arteriosclerosis), and 2 subjects in the 420 mg Q4W group (carcinoid tumour of the caecum, prostate cancer). A causal relationship of the serious adverse events to the study drug was ruled out.

Adverse events leading to study drug discontinuation occurred in 1 subject in the 70 mg Q2W group (hepatic function abnormal), 1 subject in the 140 mg Q2W group (malaise), and 2 subjects in the 420 mg Q4W group (blood CK increased/myalgia, carcinoid tumour of the caecum).

4.(iii).A.(3) Phase II/III studies

4.(iii).A.(3).1) Phase II/III studies in non-Japanese HoFH patients (Study 20110233; Attached document, 5.3.5.B.1-1; Study period, April 2012 to January 2014)

An open-label, uncontrolled study (Part A) and a randomized, double-blind, parallel-group, placebo-controlled study (Part B) were conducted at 17 centers in 10 foreign countries (Part A was conducted in 2 centers in 2 countries) in order to evaluate the efficacy and safety of evolocumab in HoFH patients (target sample size, 4-16 subjects in Part A and 51 subjects in Part B [34 in the evolocumab group and 17 in the placebo group]).

(a) Part A

Evolocumab 420 mg was administered subcutaneously Q4W during the 12-week treatment period.

The key inclusion criteria were patients aged ≥12 and ≤65 years with a confirmed genetic diagnosis of HoFH or those with a history of untreated LDL-C >500 mg/dL and with a clinical diagnosis of HoFH based on the presence of xanthoma at age <10 years or on evidence of HeFH in both parents. They also had to meet the following criteria:

- Fasting LDL-C ≥130 mg/dL at screening
- Fasting TG ≤400 mg/dL at screening
- No LDL or plasma apheresis treatment within 8 weeks before enrolment.

All of the 8 patients enrolled into this study received the study drug and were included in the safety analysis set and in the FAS. The primary efficacy analysis was based on the FAS. No patients were withdrawn from the study during the treatment period.

Table 22 shows the percent change from baseline in LDL-C (ultracentrifugation) at Week 12, the primary efficacy endpoint.

Table 22. Percent change from baseline in LDL-C (ultracentrifugation) at Week 12 (FAS)

Number of subjects	8
Baseline value (mg/dL) Value at Week 12 (mg/dL)	441.7 ± 113.3 371.1 ± 142.6
Percent change from baseline at Week 12 (%)	−16.5 ± 19.0

Mean ± SD

Safety was analyzed. Adverse events were reported in 50.0% (4 of 8) of subjects. The adverse events reported were rhinitis allergic, dyspepsia, bronchitis, and pain (1 subject each).

There were no adverse events for which a causal relationship to the study drug could not be ruled out.

There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

(b) Part B

Evolocumab 420 mg or placebo was administered subcutaneously Q4W during the 12-week treatment period.

The key inclusion criteria were patients aged ≥12 and ≤80 years with a confirmed genetic diagnosis of HoFH or those with a history of untreated LDL-C >500 mg/dL and with a clinical diagnosis of HoFH based on the presence of xanthoma at age <10 years or on evidence of HeFH in both parents. They also had to meet the following criteria:

- Fasting LDL-C ≥130 mg/dL at screening
- Fasting TG ≤400 mg/dL at screening
- No LDL or plasma apheresis within 8 weeks before enrolment.

Subjects were randomly assigned and stratified according to LDL-C levels at screening (<420 mg/dL or ≥420 mg/dL).

Of 50 randomized subjects (17 in the placebo group, 33 in the evolocumab group), 49 subjects (16 in the placebo group, 33 in the evolocumab group) received the study drug. The remaining 1 subject (in the placebo group) did not receive the study drug. All of the 49 subjects treated were included in the safety analysis set and in the FAS. The primary efficacy analysis was based on the FAS. During the study period, study treatment was discontinued in 1 subject in the placebo group because of consent withdrawal.

Table 23 shows the percent change from baseline in LDL-C levels (by ultracentrifugation and calculation) at Week 12, the primary efficacy endpoint.

Table 23. Percent change from baseline in LDL-C at Week 12 (FAS)

	LDL-C (ultracentrifugation)		LDL-C (calculation)	
	Placebo	Evolocumab	Placebo	Evolocumab
Baseline value (mg/dL)				
Number of subjects	16	33	16	33
Mean ± SD	335.8 ± 146.0	356.0 ± 134.5	335.0 ± 144.8	354.5 ± 136.4
Value at Week 12 (mg/dL)				
Number of subjects	15	29	16	29
Mean ± SD	363.8 ± 164.3	274.2 ± 161.2	357.4 ± 160.2	274.9 ± 162.1
Change at Week 12 (mg/dL)				
Number of subjects	15	29	16	29
Mean ± SD	19.5 ± 67.4	−79.1 ± 84.4	22.4 ± 64.5	−78.6 ± 82.2
Percent change at Week 12 (%)				
Number of subjects	15	29	16	29
Mean ± SD	6.11 ± 18.25	−26.07 ± 23.21	7.45 ± 19.32	−25.94 ± 22.85
Least squares mean ± SE[a]	7.88 ± 5.26	−23.05 ± 3.78	9.02 ± 5.23	−23.09 ± 3.83
Difference from placebo[a]				
Least squares mean		−30.93		−32.12
[95% CI]		[−43.86, −18.00]		[−45.05, −19.18]
		$P < 0.001$		$P < 0.001$

a: A mixed-effect model for repeated measures was used for analysis with the treatment group, LDL-C levels at screening (<420 mg/dL, ≥420 mg/dL), visit, and interaction between the treatment group and visit as fixed effects

Safety was analyzed. Adverse events were reported by 62.5% (10 of 16) of subjects in the placebo group and 36.4% (12 of 33) of subjects in the evolocumab group. Adverse events occurring in more than one subject in either group were upper respiratory tract infection (4 subjects [1 in the placebo group versus 3 in the evolocumab group]), influenza (0 subjects versus 3 subjects), gastroenteritis (0 subjects versus 2 subjects), nasopharyngitis (0 subjects versus 2 subjects), and nausea (2 subjects versus 0 subjects).

Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 12.5% (2 of 16) of subjects in the placebo group and 0.0% (0 of 33) of subjects in the evolocumab group. None of the adverse events for which a causal relationship to the study drug could not be ruled out occurred in more than one subject.

There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

4.(iii).A.(4) Phase III studies

4.(iii).A.(4).1) Phase III study in Japanese PHMD patients with high cardiovascular risk (Study 20120122; Attached document, 5.3.5A.1-11; Study period, October 2013 to June 2014)

A randomized, double-blind, parallel-group, placebo-controlled study was conducted at 52 centers in Japan in order to evaluate the efficacy and safety of evolocumab in combination with statin therapy in Japanese PHMD patients with high cardiovascular risk (target sample size, n = 90 per group [placebo or evolocumab]).

During the screening/placebo run-in/lipid stabilization period of up to 8 weeks, placebo corresponding to the volume of a Q4W dose (3 mL) was administered subcutaneously (screening/placebo run-in period), followed by oral administration of atorvastatin (5 or 20 mg) for ≥4 weeks (lipid stabilization period). During the subsequent 12 weeks, evolocumab (140 mg Q2W, 420 mg Q4W), or placebo (Q2W or Q4W) was administered subcutaneously, while the administration of atorvastatin was continued.

The key inclusion criteria were PHMD patients aged ≥20 and ≤85 years who had been receiving stable statin therapy for ≥4 weeks before the screening. They also had to meet the following criteria:

- Fasting LDL-C ≥100 mg/dL
- Fasting TG ≤400 mg/dL
- High cardiovascular risk (meeting at least one of the following)
  - History of coronary artery disease
  - Diagnosis of arteriosclerosis obliterans or peripheral arterial disease
  - History of non-cardiogenic cerebral infarction

- Diagnosis of HeFH
- Diagnosis of chronic kidney disease
- Type 2 diabetes mellitus diagnosed at ≥3 months before randomization
- Patients who met ≥3 of the following criteria: (i) men aged ≥45 years or women aged ≥55 years, (ii) history of hypertension or high blood pressure levels at screening (systolic pressure >140 mmHg or diastolic pressure >90 mmHg for at least 3 measurements), (iii) fasting blood glucose >110 mg/dL at ≥3 months before randomization, (iv) smoking history, (v) family history of early-onset (≤55 years of age in men, ≤65 years of age in women) coronary artery disease in a first-degree relative, and (vi) HDL-C <40 mg/dL.

Subjects were randomly assigned and stratified according to basal treatments (current or past diagnosis of HeFH, receiving intensive lipid-lowering therapy without diagnosis of HeFH, receiving non-intensive lipid-lowering therapy without diagnosis of HeFH) as the stratification factors.

All of 404 randomized subjects (101 in the placebo Q2W group, 101 in the placebo Q4W group, 101 in the 140 mg Q2W group, 101 in the 420 mg Q4W group) received the study drug, and were included in the safety analysis set and in the FAS. The primary efficacy analysis was based on the FAS. During the treatment period, 2 subjects in the placebo Q2W group discontinued the study treatment because of consent withdrawal and loss to follow-up.

A total of 21 HeFH patients (6 patients, 4 patients, 5 patients, 6 patients) were enrolled in the study.

Tables 24 and 25 show the mean percent change from baseline in LDL-C[9)] at Weeks 10 and 12,[10)] the primary efficacy endpoint, and the percent change in LDL-C from baseline at Week 12.

9) Calculated LDL-C values were used when calculated LDL-C value or TG did not meet the criterion (<40 mg/dL and >400 mg/dL, respectively) and, otherwise, LDL-C values measured by ultracentrifugation were used.

10) Mean of values at Week 10 and at Week 12

Table 24. Percent change from baseline in LDL-C at Weeks 10 and 12, or at Week 12 (concomitant use with atorvastatin 5 mg, FAS)

	Q2W		Q4W	
	Placebo	140 mg	Placebo	420 mg
Baseline value (mg/dL)				
Number of subjects	49	50	50	50
Mean ± SD	115.7 ± 26.0	121.9 ± 44.6	114.0 ± 29.2	118.8 ± 36.6
Value at Week 10 (mg/dL)				
Number of subjects	49	50	49	50
Mean ± SD	111.9 ± 25.6	31.1 ± 25.8	113.1 ± 31.4	28.7 ± 19.4
Value at Week 12 (mg/dL)				
Number of subjects	49	49	48	50
Mean ± SD	114.1 ± 25.1	30.6 ± 21.5	117.7 ± 38.4	38.6 ± 17.7
Mean change at Weeks 10 and 12 (mg/dL)				
Number of subjects	49	50	49	50
Mean ± SD	−2.6 ± 15.5	−91.1 ± 30.8	1.0 ± 14.7	−85.2 ± 28.3
Mean percent change at Weeks 10 and 12 (%)				
Number of subjects	49	50	49	50
Mean ± SD	−1.28 ± 12.76	−75.28 ± 9.87	0.80 ± 12.22	−71.62 ± 10.24
Least squares mean ± SE[a]	0.27 ± 2.21	−73.70 ± 2.26	3.91 ± 2.09	−68.98 ± 2.02
Difference from placebo[a]				
Least squares mean		−73.97		−72.89
[95% CI]		[−78.54, −69.41]		[−77.22, −68.57]
		$P < 0.001$		$P < 0.001$
Change at Week 12 (mg/dL)				
Number of subjects	49	49	48	50
Mean ± SD	−1.5 ± 17.2	−92.0 ± 33.9	3.9 ± 16.2	−80.3 ± 27.1
Percent change at Week 12 (%)				
Number of subjects	49	49	48	50
Mean ± SD	−0.28 ± 15.04	−75.16 ± 11.60	2.67 ± 13.53	−67.26 ± 9.67
Least squares mean ± SE[a]	1.28 ± 2.43	−73.57 ± 2.48	5.29 ± 2.19	−64.62 ± 2.12
Difference from placebo[a]				
Least squares mean		−74.85		−69.91
[95% CI]		[−80.22, −69.47]		[−74.60, −65.23]
		$P < 0.001$		$P < 0.001$

a: A mixed-effect model for repeated measures was used for analysis with the treatment group, stratification factors, visit, and interaction between the treatment group and visit as fixed effects

Table 25. Percent change from baseline in LDL-C at Weeks 10 and 12, or at Week 12 (concomitant use with atorvastatin 20 mg, FAS)

	Q2W		Q4W	
	Placebo	140 mg	Placebo	420 mg
Baseline value (mg/dL)				
Number of subjects	52	51	51	51
Mean ± SD	90.9 ± 25.5	95.8 ± 23.6	90.7 ± 20.8	98.0 ± 25.6
Value at Week 10 (mg/dL)				
Number of subjects	49	49	51	51
Mean ± SD	88.9 ± 26.2	25.0 ± 12.8	89.0 ± 18.0	17.4 ± 10.7
Value at Week 12 (mg/dL)				
Number of subjects	49	50	50	51
Mean ± SD	91.3 ± 23.2	26.8 ± 16.4	87.4 ± 22.5	29.4 ± 16.5
Mean change at Weeks 10 and 12 (mg/dL)				
Number of subjects	49	50	51	51
Mean ± SD	−1.2 ± 14.0	−69.3 ± 21.5	−2.4 ± 12.0	−74.6 ± 23.9
Mean percent change at Weeks 10 and 12 (%)				
Number of subjects	49	50	51	51
Mean ± SD	0.96 ± 20.61	−72.55 ± 14.02	−1.28 ± 13.26	−75.61 ± 9.98
Least squares mean ± SE[a]	−0.42 ± 3.26	−74.82 ± 3.26	−2.67 ± 2.31	−76.93 ± 2.24
Difference from placebo[a]				
Least squares mean		−74.41		−74.27
[95% CI]		[−81.21, −67.61]		[−78.93, −69.60]
		$P < 0.001$		$P < 0.001$
Change at Week 12 (mg/dL)				
Number of subjects	49	50	50	51
Mean ± SD	0.0 ± 16.5	−69.1 ± 21.5	−2.8 ± 14.5	−68.6 ± 26.2
Percent change at Week 12 (%)				
Number of subjects	49	50	50	51
Mean ± SD	2.77 ± 23.94	−72.48 ± 14.19	−1.94 ± 15.65	−69.05 ± 14.61
Least squares mean ± SE[a]	1.39 ± 3.51	−74.46 ± 3.50	−3.49 ± 2.67	−70.36 ± 2.61
Difference from placebo[a]				
Least squares mean		−75.85		−66.87
[95% CI]		[−83.55, −68.15]		[−72.88, −60.87]
		$P < 0.001$		$P < 0.001$

a: A mixed-effect model for repeated measures was used for analysis with the treatment group, stratification factors, visit time, and interaction between the treatment group and visit as fixed effects

Tables 26 shows percent changes from baseline in TC, HDL-C, non-HDL-C, and TG at Week 12 as the secondary endpoints.

Table 26. Percent change from baseline in lipid parameters at Week 12 (FAS)

	Q2W		Q4W	
	Placebo	140 mg	Placebo	420 mg
TC				
Baseline value (mg/dL)	101 188.3 ± 33.6	101 193.9 ± 41.6	101 186.4 ± 33.7	101 190.6 ± 36.0
Value at Week 12 (mg/dL)	98 185.9 ± 31.5	99 107.5 ± 23.9	98 184.6 ± 40.0	101 112.4 ± 23.9
Percent change at Week 12 (%)	98 −0.89 ± 12.26	99 −43.97 ± 10.18	98 −0.70 ± 9.04	101 −40.60 ± 9.36
HDL-C				
Baseline value (mg/dL)	101 58.6 ± 14.5	101 57.2 ± 13.6	101 57.1 ± 13.0	101 55.5 ± 14.8
Value at Week 12 (mg/dL)	98 56.1 ± 14.2	99 63.5 ± 15.0	98 55.7 ± 13.0	101 61.1 ± 15.9
Percent change at Week 12 (%)	98 −3.95 ± 14.23	99 11.32 ± 16.28	98 −1.53 ± 13.42	101 11.21 ± 13.65
TG				
Baseline value (mg/dL)	101 134.4 ± 57.2	101 147.7 ± 123.9	101 138.4 ± 91.0	101 134.2 ± 58.5
Value at Week 12 (mg/dL)	98 136.9 ± 74.5	99 105.9 ± 68.4	98 133.0 ± 59.0	101 112.6 ± 74.6
Percent change at Week 12 (%)	98 4.46 ± 40.47	99 −18.78 ± 36.33	98 4.01 ± 33.16	101 −14.39 ± 32.79
non-HDL-C				
Baseline value (mg/dL)	101 129.7 ± 31.7	101 136.7 ± 42.9	101 129.2 ± 30.9	101 135.1 ± 36.9
Value at Week 12 (mg/dL)	98 129.8 ± 31.7	99 44.0 ± 22.6	98 128.9 ± 37.1	101 51.2 ± 22.1
Percent change at Week 12 (%)	98 0.79 ± 15.86	99 −68.03 ± 11.57	98 0.04 ± 12.37	101 −62.17 ± 11.07

Upper box, number of subjects; lower box, mean ± SD

Safety was analyzed. adverse events were reported in 49.5% (50 of 101) of subjects in the placebo Q2W group, 52.5% (53 of 101) of subjects in the placebo Q4W group, 48.5% (49 of 101) of subjects in the 140 mg Q2W group, and 44.6% (45 of 101) of subjects in the 420 mg Q4W group. Table 27 shows adverse events occurring in ≥3% of subjects in any group.

Table 27. Adverse events occurring in ≥3% of subjects in any group (FAS)

	Q2W		Q4W	
	Placebo	140 mg	Placebo	420 mg
Number of subjects	101	101	101	101
Nasopharyngitis	14.9 (15)	18.8 (19)	20.8 (21)	14.9 (15)
Upper respiratory tract inflammation	1.0 (1)	3.0 (3)	0 (0)	1.0 (1)
Pharyngitis	3.0 (3)	3.0 (3)	2.0 (2)	2.0 (2)
Upper respiratory tract infection	0 (0)	3.0 (3)	3.0 (3)	0 (0)
Diabetes mellitus	0 (0)	2.0 (2)	4.0 (4)	2.0 (2)
Gastroenteritis	2.0 (2)	1.0 (1)	0 (0)	5.0 (5)
Back pain	0 (0)	1.0 (1)	3.0 (3)	2.0 (2)
Contusion	0 (0)	1.0 (1)	3.0 (3)	0 (0)
Type 2 diabetes mellitus	1.0 (1)	0 (0)	3.0 (3)	1.0 (1)
Vertigo	3.0 (3)	0 (0)	0 (0)	0 (0)

% (number of subjects)

Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 5.0% (5 of 101) of subjects in the placebo Q2W group, 4.0% (4 of 101) of subjects in the placebo Q4W group, 1.0% (1 of 101) of subjects in the 140 mg Q2W group, and 1.0% (1 of 101) of subjects in the 420 mg Q4W group. None of the adverse events for which a causal relationship to the study drug could not be ruled out occurred in ≥3% of subjects in any group.

No deaths were reported. Serious adverse events were reported by 2 subjects in the placebo Q2W group (brain stem infarction, epilepsy), 3 subjects in the placebo Q4W group (contusion, rotator cuff syndrome, endometrial cancer), and 1 subject in the 420 mg Q4W group (pneumonia bacterial). A causal relationship to the study drug was ruled out for all of the serious adverse events.

An adverse event leading to study drug discontinuation occurred in 1 subject in the placebo Q2W group (brain stem infarction).

4.(iii).A.(4).2) Long-term extension study (a) (Study 20110110, Attached document 5.3.5A.1-12; Study period, October 2011 – ongoing [data cut-off, [redacted]])

A randomized, open-label, parallel-group, comparative study in patients who had completed one of the Japanese or foreign parent studies[11] was conducted at 189 centers in 18 countries including Japan in order to evaluate the long-term safety and efficacy of evolocumab in PHMD patients (target sample size, 1600 subjects).

After the completion of the parent study, subjects proceeded to a 52-week controlled study, during which they received the standard of care (SoC)[12] plus evolocumab 420 mg SC Q4W (evolocumab group) or SoC alone (control group). After the completion of the controlled study, all subjects were to receive of evolocumab 420 mg SC Q4W for 4 years. At 12 weeks after the start of treatment in the controlled study, the investigator was allowed to change the basal therapy according to SoC based on the disclosed LDL-C level, but prohibited from reducing the dose of statins according to the disclosed LDL-C level.

The key inclusion criteria were patients who had completed a qualifying parent study.

Subjects were randomized to treatment (to the evolocumab group and to the control group at 2:1 ratio) and stratified according to the treatment regimen to which they had been assigned in the parent study.

(a) Results for Year 1 (Year 1 SoC-controlled period)

a) Overall study results

Of 1648 subjects who had completed one of the parent studies, 1324 subjects proceeded to the extension study. All of the 1324 randomized subjects (n = 882 in the evolocumab group versus n = 442 in the control group) were included in the efficacy and safety analyses. As of [redacted], 1006 subjects (n = 681 versus n = 325) completed the Year 1 SoC-controlled period and 217 subjects (n = 144 versus n = 73) are still undergoing treatment in the ongoing study. Study treatment was discontinued in 101 subjects (n = 57 versus n = 44). The main reasons for the discontinuation were consent withdrawal in 57 subjects (n = 33 versus n = 24), other reasons in 25 subjects (n = 15 versus n = 10), and loss to follow-up in 15 subjects (n = 7 versus n = 8).

Table 28 shows the percent change from baseline in LDL-C (calculation) at Weeks 12 and 52 in the parent study as the efficacy endpoint.

Table 28. Percent change from baseline in LDL-C (calculation) at Weeks 12 and 52 in parent study

Treatment group in parent study	Evolocumab		Control	
Treatment group in extension study	Evolocumab	Control	Evolocumab	Control
Baseline value in parent study				
Number of subjects	643	322	239	120
Mean ± SD	137.5 ± 38.3	141.9 ± 40.1	138.2 ± 34.4	146.8 ± 35.9
Percent change at Week 12 (%)				
Number of subjects	624	305	234	116
Mean ± SD	−59.12 ± 19.53	−5.13 ± 18.11	−58.49 ± 21.34	−2.49 ± 21.88
Percent change at Week 52 (%)				
Number of subjects	525	247	185	95
Mean ± SD	−54.42 ± 23.80	−3.32 ± 21.27	−54.91 ± 23.95	−2.59 ± 24.28

[11] A foreign phase II study in HeFH patients (Study 20090158), a foreign phase II study in HC patients intolerant to statins (Study 20090159), foreign phase II studies in HC patients (Studies 20101154 and 20101155), and Study 20110231

[12] The lipid-lowering therapy performed in the parent study according to the local standard of care

Safety was analyzed. Adverse events were reported by 81.9% (722 of 882) of subjects in the evolocumab group and 73.3% (324 of 442) of subjects in the control group. Adverse events reported by ≥5% of subjects in either group were nasopharyngitis (16.2% in the evolocumab group versus 13.6% in the control group), upper respiratory tract infection (8.0% versus 6.6%), back pain (7.0% versus 4.8%), arthralgia (6.6% versus 4.1%), influenza (6.6% versus 5.2%), headache (6.1% versus 2.7%), hypertension (6.0% versus 4.3%), bronchitis (5.4% versus 4.1%), and pain in extremity (5.0% versus 3.2%).

Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 12.7% (112 of 882) of subjects in the evolocumab group. None of the adverse events for which a causal relationship to the study drug could not be ruled out occurred in ≥5% of subjects.

Death occurred in 3 subjects (myocardial infarction in the evolocumab group, pulmonary embolism and unknown cause of death in the control group). Serious adverse events were reported by 7.6% (67 of 882) of subjects in the evolocumab group and 6.8% (30 of 442) of subjects in the control group. No serious adverse events occurred in ≥1% of subjects in either group.

Adverse events leading to study drug discontinuation occurred in 3.1% (27 of 882) of subjects in the evolocumab group. Adverse events leading to study drug discontinuation that occurred in more than one subject were arthralgia (0.3%) and myalgia (0.2%).

b) Results in Japanese population

Of 301 subjects who had completed Study 20110231, 219 subjects proceeded to the extension study and were randomized. All of the 219 randomized subjects (n = 146 in the evolocumab group versus n = 73 in the control group) were included in the efficacy and safety analyses. As of [redacted], none of the subjects completed Year 1 of the study, and 217 subjects (n = 144 versus n = 73) are still undergoing treatment in the ongoing study (for Year 1). Two subjects (n = 2 versus n = 0) discontinued the study; both withdrew the consent.

Table 29 shows the percent change from baseline in LDL-C (calculation) at Weeks 12 and 52 in the parent study as the efficacy endpoint.

Table 29. Percent change from baseline in LDL-C (calculation) at Weeks 12 and 52 in parent study

Parent study	Evolocumab		Control	
Extension study	Evolocumab	Control	Evolocumab	Control
Baseline value in parent study				
Number of subjects	99	49	47	24
Mean ± SD	137.1 ± 22.2	145.9 ± 25.1	142.1 ± 21.4	146.4 ± 17.3
Percent change at Week 12 (%)				
Number of subjects	98	48	47	24
Mean ± SD	−70.46 ± 11.43	−2.18 ± 13.70	−69.32 ± 11.13	−1.43 ± 11.82
Percent change at Week 52 (%)				
Number of subjects	22	9	12	7
Mean ± SD	−65.44 ± 24.10	10.52 ± 12.51	−70.66 ± 9.83	−1.39 ± 13.83

Safety was analyzed. Adverse events were reported by 79.5% (116 of 146) of subjects in the evolocumab group and 75.3% (55 of 73) of subjects in the control group. Adverse events reported by ≥5% of subjects in either group were nasopharyngitis (31.5% in the evolocumab group, 34.2% in the control group), diabetes mellitus (8.9%, 1.4%), back pain (6.2%, 0%), and contusion (4.1%, 6.8%).

Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 10.3% (15 of 146) of subjects in the evolocumab group. None of the adverse events for which a causal relationship to the study drug could not be ruled out occurred in ≥5% of subjects in this group.

No deaths were reported. Serious adverse events were reported by 7.5% (11 of 146) of subjects in the evolocumab group and 6.8% (5 of 73) of subjects in the control group. No serious adverse events occurred in more than one subjects in either group.

Adverse events leading to study drug discontinuation occurred in 2 subjects (gastric cancer, lung neoplasm malignant) in the evolocumab group and none in the control group.

(b) Results for Year 2+ period (open-label period) (overall study results)

As of [redacted], of 1006 subjects (n = 681 in the evolocumab group versus n = 325 in the control group) who had completed Year 1 of the study, 937 subjects (n = 632 versus n = 305) proceeded to the second year and onward (Year 2+) period of the study to receive evolocumab. They were included in the efficacy and safety analyses. Study treatment was discontinued in 44 subjects (n = 30 versus n = 14), with the main reasons being consent withdrawal in 20 subjects (n = 13 versus n = 7) and loss to follow-up in 14 subjects (n = 9 versus n = 5).

Table 30 shows the percent change in LDL-C (calculation) from baseline at Week 124 in the parent study as the efficacy endpoint.

Table 30. Percent change from baseline in LDL-C level (calculation) at Week 124 in the parent study

Treatment group in the Year 1 period	Evolocumab	Control
Baseline value in parent study (mg/dL)		
Number of subjects	632	305
Mean ± SD	138.2 ± 40.3	143.3 ± 42.5
Percent change at Week 124 (%)		
Number of subjects	39	18
Mean ± SD	−49.87 ± 27.38	−52.81 ± 30.07

Safety was analyzed. Adverse events were reported by 75.7% (709 of 937) of subjects, and adverse events reported by ≥5% of subjects were nasopharyngitis (12.0%), upper respiratory tract infection (7.8%), arthralgia (6.8%), back pain (6.7%), hypertension (5.5%), cough (5.5%), bronchitis (5.4%), and sinusitis (5.2%).

Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 5.2% (49 of 937) of subjects. None of the adverse events for which a causal relationship to the study drug could not be ruled out occurred in ≥5% of subjects.

Death occurred in 2 subjects (cholangiocarcinoma, peripheral ischaemia). Serious adverse events occurred in 7.3% (68 of 937) of subjects. Serious adverse events occurring in ≥3 subjects were pneumonia (4 subjects), non-cardiac chest pain (4 subjects), and angina pectoris (3 subjects).

Adverse events leading to study drug discontinuation occurred in 1.1% (10 of 937) of subjects.

4.(iii).A.(4).3) Long-term extension study (b) (Study 20120138, Attached document 5.3.5A.1-13; Study period, ongoing since April 2013 [data cut-off, [redacted] ([redacted] only for Japanese subjects)])

A randomized, open-label, parallel-group, comparative study in patients who had completed one of the Japanese or foreign parent studies[13)] was conducted at 450 centers in 24 countries including Japan in order to evaluate the long-term safety and efficacy of evolocumab in PHMD patients (target sample size, 3500 subjects).

After the completion of the parent study, subjects proceeded to a 48-week controlled study, during which they received SoC alone (control group) or evolocumab 140 mg SC Q2W or 420 mg SC Q4W plus SoC.

13) A phase III study in patients with hyperlipidemia (Study 20110109), a phase III study in patients with 10-year Framingham Risk Score ≤10% (Study 20110114), a phase III study in PHMD patients (Study 20110115), a phase III study in HC patients intolerant to statins (Study 20110116), a phase III study in HeFH patients (Study 20110117), phase III studies in PHMD patients (Studies 20120348 and 20120356), and Study 20120122

During the 48-week period after the end of the controlled study, all subjects received evolocumab 140 mg SC Q2W or 420 mg SC Q4W plus SoC. At 12 weeks after the start of treatment in Year 1, the investigator was allowed to change SoC based on the disclosed LDL-C level.

The key inclusion criteria were patients who had completed a qualifying parent study.

Subjects were randomly assigned to the evolocumab group or the control group at a 2:1 ratio and stratified according to the parent study and the dosage regimen in the parent study (Q2W or Q4W).

(a) Results for Year 1 (Year 1 SoC-controlled period)

a) Overall study results

Of 4360 subjects who had completed the parent study, 3122 subjects proceeded to the extension study. Of 3121 randomized subjects (n = 2080 in the evolocumab group versus n = 1041 in the control group), 2928 subjects (n = 1951 versus n = 977) were included in the efficacy safety analyses for the Year 1 period of the study. As of [redacted], 27 subjects (n = 16 versus n = 11) completed Year 1 of the study and 2866 subjects (n = 1908 versus n = 958) are still undergoing treatment in the ongoing study (for Year 1). Study treatment was discontinued in 35 subjects (n = 27 versus n = 8), with the main reason being consent withdrawal in 23 subjects (n = 21 versus n = 2).

Table 31 shows the percent change from baseline in LDL-C (calculation or ultracentrifugation[14)]) at Weeks 12 and 48 in the parent study as the efficacy endpoint.

Table 31. Percent change from baseline in LDL-C at Weeks 12 and 48 in the parent study

Parent study	Evolocumab		Control	
Extension study	Evolocumab	Control	Evolocumab	Control
Baseline value in parent study				
Number of subjects	1247	625	704	352
Mean ± SD	125.9 ± 48.1	125.4 ± 48.2	123.1 ± 44.1	121.0 ± 44.8
Percent change at Week 12 (%)				
Number of subjects	1191	594	676	323
Mean ± SD	−53.0 ± 27.03	6.9 ± 35.80	−52.2 ± 32.25	13.8 ± 41.43
Percent change at Week 48 (%)				
Number of subjects	3	5	2	1
Mean ± SD	−60.5 ± 21.30	16.4 ± 20.65	−46.6 ± 6.94	84.6

Safety was analyzed. Adverse events were reported by 50.6% (988 of 1951) of subjects in the evolocumab group and 46.7% (456 of 977) of subjects in the control group. Adverse events reported by ≥2% of subjects in either group were nasopharyngitis (5.1% in the evolocumab group versus 5.3% in the control group), upper respiratory tract infection (2.5% versus 2.9%), myalgia (2.1% versus 1.7%), arthralgia (2.0% versus 1.8%), hypertension (1.8% versus 2.1%), sinusitis (1.6% versus 2.3%), and bronchitis (1.4% versus 2.6%).

Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 7.4% (145 of 1951) of subjects in the evolocumab group. None of the adverse events for which a causal relationship to the study drug could not be ruled out occurred in ≥5% of subjects.

Death occurred in 4 subjects (myocardial infarction and sudden death in the evolocumab group, *Clostridium difficile* infection and lung neoplasm malignant in the control group). Serious adverse events were reported by 4.3% (83 of 1951) of subjects in the evolocumab group and 4.5% (44 of 977) of subjects in the control group. No serious adverse events occurred in ≥1% of subjects in either group.

Adverse events leading to study drug discontinuation occurred in 1.6% (31 of 1951) of subjects in the evolocumab group. Adverse events leading to study drug discontinuation occurring in more than one subject were myalgia in 5 subjects; injection site pain in 3 subjects; and fatigue, injection site erythema, urticaria, injection site hypersensitivity, injection site swelling, and insomnia in 2 subjects each.

14) Calculated LDL-C values were used when calculated LDL-C value or TG did not meet the criterion (<40 mg/dL and >400 mg/dL, respectively) and, otherwise, LDL-C values measured by the ultracentrifugation method were used.

b) Results in Japanese population (data cut-off, [redacted])

Of 402 subjects who had completed Study 20120122, 337 subjects proceeded to the extension study. All of the 337 randomized subjects (n = 224 in the evolocumab group versus n = 113 in the control group) were included in the efficacy safety analyses for the Year 1 period. As of [redacted], 298 subjects (n = 200 versus n = 98) completed the first year of the study, and 18 subjects (n = 11 versus n = 7) are still undergoing treatment in the ongoing study (for Year 1). Study treatment was discontinued in 21 subjects (n = 13 versus n = 8) because of consent withdrawal.

Table 32 shows the percent change from baseline in LDL-C (calculation) at Weeks 12 and 48 in the parent study as the efficacy endpoint.

Table 32. Percent change from baseline in LDL-C (calculation) at Weeks 12 and 48 in the parent study

Parent study	Evolocumab		Control	
Extension study	Evolocumab	Control	Evolocumab	Control
Baseline value in parent study				
Number of subjects	120	55	104	58
Mean ± SD	106.8 ± 34.3	110.8 ± 30.6	105.2 ± 29.6	100.1 ± 27.4
Percent change at Week 12 (%)				
Number of subjects	115	53	98	57
Mean ± SD	−71.00 ± 16.83	5.79 ± 27.67	−68.79 ± 23.34	16.50 ± 37.89
Percent change at Week 48 (%)				
Number of subjects	107	48	87	48
Mean ± SD	−66.01 ± 29.46	16.86 ± 29.90	−64.00 ± 31.98	20.47 ± 28.09

Safety was analyzed. Adverse events were reported by 69.6% (156 of 224) of subjects in the evolocumab group and 67.3% (76 of 113) of subjects in the control group. Adverse events reported by ≥5% of subjects in any of the groups in the Japanese population were nasopharyngitis (21.0% in the evolocumab group versus 22.1% in the control group), bronchitis (6.3% versus 4.4%), diabetes mellitus (6.3% versus 2.7%), and pharyngitis (2.2% versus 5.3%).

Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 6.7% (15 of 224) of subjects in the evolocumab group. None of the adverse events for which a causal relationship to the study drug could not be ruled out occurred in ≥5% of subjects.

No deaths were reported. Serious adverse events occurred in 5.8% (13 of 224) of subjects in the evolocumab group and 11.5% (13 of 113) of subjects in the control group. No serious adverse events occurred more than one subject in any group.

Adverse events leading to study drug discontinuation occurred in 1 of 224 subjects (0.4%, rash pruritic) in the evolocumab group.

4.(iii).A.(4).4) Long-term extension study in HoFH and severe FH patients (Study 20110271, Attached document 5.3.5.B.2-1; Study period, ongoing since June 2012 [data cut-off, [redacted]])

An open-label study in patients who had completed one of the parent studies was conducted at 38 centers in 18 countries or regions including Japan in order to evaluate the long-term safety and efficacy of evolocumab in patients with HoFH or severe FH (target sample size, 310 subjects).

Evolocumab was to be administered for up to 5 years. Subjects who had not been on apheresis at enrollment or within 8 weeks before enrollment were to start treatment with evolocumab at 420 mg Q4W, and subjects who had been on apheresis at enrollment were to start treatment with evolocumab at 420 mg Q2W. At the Week 12 or 24 visit, or at any other visits, the change of the dose frequency (to 420 mg Q4W or 420 mg Q2W) was allowed by referring to LDL-C or PCSK9 concentrations.

When a <5% reduction from baseline in LDL-C was achieved and unbound PCSK9 serum concentrations was <100 ng/mL, discontinuation of evolocumab was allowed. When unbound PCSK9

serum concentrations were ≥100 ng/mL in subjects receiving 420 mg Q4W, switching to 420 mg Q2W was allowed. When a ≥5% reduction from baseline in LDL-C was achieved in apheresis subjects receiving 420 mg Q2W, it was allowed to switch the dosage regimen to 420 mg Q4W.

The key inclusion criteria were patients aged ≥12 and ≤ 80 years with HoFH or severe FH[15)] who met the following criteria:

- Fasting TG ≤400 mg/dL at screening
- LDL-C levels ≥100 mg/dL in non-apheresis subjects with a diagnosis of coronary artery disease or those with similar risk factors, or LDL-C levels ≥130 mg/dL in non-apheresis subjects with no diagnosis of coronary artery disease or those with similar risk factors.

(a) Overall study results

Evolocumab was administered to 242 subjects and all of the subjects were included in the efficacy the safety analyses. Table 33 shows the breakdown of the subjects. Study treatment discontinued in 11 subjects, and the main reasons were physician's discretion (6 subjects), subject's request (2 subjects), and adverse events (2 subjects).

Table 33. Breakdown of subjects treated with evolocumab

	Patients with HoFH	Patients with severe FH	Total
Apheresis patients	n = 34	n = 16	n = 50
Non-apheresis patients	n = 66	n = 126	n = 192
Total	n = 100	n = 142	n = 242

Table 34 shows the percent change from baseline in LDL-C (ultracentrifugation) at Weeks 12, 24, and 36.

Table 34. Percent change from baseline in LDL-C (ultracentrifugation) at Weeks 12, 24, and 36

	Patients with HoFH		Patients with severe FH	
	Apheresis patients	Non-apheresis patients	Apheresis patients	Non-apheresis patients
Baseline value				
Number of subjects	34	66	16	125
Mean ± SD	286.3 ± 100.1	336.9 ± 138.9	199.1 ± 43.3	183.0 ± 63.6
Percent change at Week 12 (%)				
Number of subjects	31	63	7	109
Mean ± SD	−16.51 ± 27.29	−23.10 ± 22.05	−64.84 ± 18.52	−51.65 ± 16.42
Percent change at Week 24 (%)				
Number of subjects	22	45	0	17
Mean ± SD	−13.70 ± 37.79	−28.07 ± 22.13	-	−37.87 ± 35.93
Percent change at Week 36 (%)				
Number of subjects	13	32	0	8
Mean ± SD	−9.05 ± 28.01	−29.78 ± 24.15	-	−50.24 ± 12.78

Safety analysis revealed that adverse events were reported by 61.2% (148 of 242) of subjects. Adverse events reported by ≥10% of subjects in any group (except for apheresis patients with severe FH) are as shown in Table 35.

15) HoFH: Patients who shifted from Study 20110233, patients who did not meet the inclusion criteria for Study 20110233 (had unexamined gene mutation or were receiving apheresis), and patients who participated directly in the extension study after the end of Study 20110233
Severe FH: Patients who shifted from other parent studies and patients who directly participated in the extension study

Table 35. Adverse events reported by ≥10% of subjects in any group

	Patients with HoFH		Patients with severe FH	
	Apheresis patients	Non-apheresis patients	Apheresis patients	Non-apheresis patients
Number of subjects	34	66	16	126
Nasopharyngitis	14.7 (5)	6.1 (4)	0 (0)	9.5 (12)
Injection site pain	11.8 (4)	0 (0)	0 (0)	1.6 (2)
Injection site erythema	11.8 (4)	0 (0)	12.5 (2)	3.2 (4)
Vomiting	11.8 (4)	0 (0)	0 (0)	1.6 (2)

% (number of subjects)

Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 17.8% (43 of 242) of subjects. The adverse event for which a causal relationship to the study drug could not be ruled out and which occurred in ≥3% of subjects was injection site erythema (3.3% [8 of 242 subjects]; 4 patients with HoFH, 4 patients with severe FH).

No deaths were reported. Serious adverse events occurred in 10 patients with HoFH (aortic stenosis/coronary artery disease, angina pectoris, aortic valve disease, arteriovenous fistula, thrombosis, carotid artery occlusion, chest pain, coronary artery occlusion, haematuria, myocardial ischaemia, non-cardiac chest pain) and in 3 patients with severe FH (angina pectoris, colitis, uterine prolapse). A causal relationship of myocardial ischaemia to evolocumab could not be ruled out, but the outcome of the adverse event was reported as resolved.

Adverse events leading to study drug discontinuation occurred in 1 patient with HoFH (rash) and in 1 patient with severe FH (glossitis/hyperhidrosis/malaise/muscle spasms/myalgia/nasal congestion/pyrexia).

(b) Results in Japanese population

Evolocumab was administered to 8 subjects and all of the subjects were included in the efficacy analyses. Table 36 shows the breakdown of the subjects. Study treatment discontinued in 2 subjects because of physician's discretion (1 subject) and an adverse event (1 subject).

Table 36. Breakdown of subjects receiving evolocumab

	Patients with HoFH	Patients with severe FH	Total
Apheresis patients	n = 5	n = 0	n = 5
Non-apheresis patients	n = 2	n = 1	n = 3
Total	n = 7	n = 1	n = 8

Table 37 shows the percent change from baseline in LDL-C (ultracentrifugation) at Weeks 12, 24, and 36.

Table 37. Percent change from baseline in LDL-C (ultracentrifugation) at Weeks 12, 24, and 36

	Apheresis patients	Non-apheresis patients
Baseline value		
Number of subjects	5	3
Mean ± SD	217.6 ± 63.7	167.3 ± 12.7
Percent change at Week 12 (%)		
Number of subjects	5	3
Mean ± SD	−42.50 ± 36.87	−58.97 ± 33.99
Percent change at Week 24 (%)		
Number of subjects	3	3
Mean ± SD	−33.36 ± 36.19	−28.28 ± 65.79
Percent change at Week 36 (%)		
Number of subjects	2	2
Mean ± SD	−56.66 ± 2.96	−65.40 ± 0.99

Safety analysis revealed that adverse events were reported by 100.0% (8 of 8) of subjects. Adverse events occurring in more than one subject were carotid intima-media thickness increased (62.5% [5 of 8] of subjects) and nasopharyngitis (25.0% [2 of 8] of subjects).

Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 62.5% (5 of 8) of subjects. The adverse event for which a causal relationship to the study drug could not be ruled out and which occurred in more than one subject was carotid intima-media thickness increased (62.5% [5 of 8] of subjects).

No deaths were reported. A serious adverse event occurred in 1 patient with HoFH (myocardial ischaemia) but the outcome was reported as resolved.

Adverse events leading to study drug discontinuation occurred in 1 patient with severe FH (glossitis/hyperhidrosis/malaise/muscle spasms/myalgia/nasal congestion/pyrexia).

4.(iii).B. Outline of the review by PMDA

4.(iii).B.(1) Clinical positioning

The applicant's explanation on the clinical positioning of Repatha SC Injection 140 mg Syringe and Repatha SC Injection 140 mg Pen:
In patients with high blood LDL-C levels or with high cardiovascular risk, LDL-C-lowering therapy is performed to reduce the risk of cardiovascular events. Although currently available lipid-lowering therapies such as statins are effective, they may not decrease LDL-C levels adequately. The results of Japanese and foreign clinical studies support the efficacy and safety of evolocumab in HC and FH patients, based on which the applicant considers that evolocumab offers a new therapeutic option for lipid-lowering therapy.

PMDA's view:
Hyper-LDL-cholesterolemia is one of the major risk factors for arteriosclerotic disease. The Clinical Practice Guideline for Dyslipidemia (2013) published by the Japan Atherosclerosis Society defines the target LDL-C levels depending on patient characteristics. FH patients have a high risk of coronary artery disease, and the guideline recommends a strict regimen. According to currently available Japanese and foreign guidelines, statins are positioned as the first-line therapy for HC patients. The Japanese phase III study demonstrated the add-on effect of evolocumab to statin therapy in lowering LDL-C as well as the safety of evolocumab. Taking account of the above, it is appropriate to use evolocumab in combination with conventional therapies including statins for patients who have had an inadequate response to statin therapy. The details will be reviewed in "4.(iii).B.(2) Indications."

4.(iii).B.(2) Indications

The applicant's explanation on the appropriateness of the target patients and the proposed indication of evolocumab:
As stated in the Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases (*Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2012*, Japan Atherosclerosis Society, 2012, [Guidelines on arteriosclerosis]), statins are the first-line therapy for HC patients. Evolocumab is intended to be used in patients with HC, including patients with FH, who have had an inadequate response to a statin alone or to conventional therapies with statins in combination with other lipid-lowering therapies. Evolocumab is thus positioned as an add-on therapy for lowering LDL-C levels. Whether an add-on therapy is given to patients on statin therapy is decided based on the extent of LDL-C elevation, the risk of cardiovascular events, and the benefit-risk balance of therapy in individual patients assessed by the physician. The extent of absolute risks should be determined based on the clinical consensus and on the findings obtained in routine clinical practice. Evolocumab is indicated in patients on statin therapy who are expected to obtain benefits from further reduction in LDL-C levels. Data obtained during the development process of evolocumab have shown that evolocumab lowered LDL-C levels in HC and FH patients in whom LDL-C levels could not be controlled by statin therapy, and that evolocumab has a favorable safety profile. With the above taken into account, the proposed indications is "Hypercholesterolemia, heterozygous familial hypercholesterolemia, and homozygous familial hypercholesterolemia. The product should be used only in patients who have had an inadequate response to conventional therapies." Since evolocumab is indicated in patients who have already started

statin therapy to reduce cardiovascular risk, the target patients should be more clearly defined for proper use of evolocumab. Therefore, the following specific information will be included in the "Precautions for Indications" section in order to identify the eligibility of patients with cardiovascular risk factors for evolocumab therapy.

Revised indications proposed by the applicant (Underline denotes the addition to the initially proposed indication)

[Indications]
Hypercholesterolemia and heterozygous familial hypercholesterolemia
Homozygous familial hypercholesterolemia
The product should be used only in patients who have had an inadequate response to conventional therapies.

[Precautions for Indications]
1. Detailed tests should be performed to confirm a diagnosis of hypercholesterolemia, heterozygous familial hypercholesterolemia, or homozygous familial hypercholesterolemia. Use of evolocumab should be considered only for patients with a definitive diagnosis of any of the above diseases.
2. Prior to the use of evolocumab in patients with hypercholesterolemia (nonfamilial), the patients should be checked for cardiovascular disease or its risk factors. Cardiovascular disease risk factors include hypertension, diabetes mellitus, hypo-high-density lipoproteinemia, smoking, chronic kidney disease, family history, age (elderly), and sex (male).
3. When patients have had an inadequate response to lipid-lowering drug therapy with HMG-CoA reductase inhibitors as the basal therapeutic agents, the use of evolocumab should be considered.
4. The efficacy and safety of evolocumab monotherapy have not been established in the Japanese population.

PMDA's view:
The current standard drug therapy for HC patients is statins alone or statins with oral drugs with different mechanism of action. The efficacy and safety of evolocumab in Japanese patients were evaluated based on the results of the Japanese phase II and III studies in which evolocumab was used in combination with statins. The results of these studies were included in this application. Taking account of the above, evolocumab should be used at least in patients who have had an inadequate response to conventional therapies including statins. Not only the evaluation of changes in individual lipid parameters but also the assessment of the reduction in actual cardiovascular events are currently important for the treatment of dyslipidemia. However, at present, there are no available data supporting the cardiovascular risk-reduction effect of evolocumab. Also, the mean LDL-C level at Week 10 to Week 12 decreased to approximately 30 mg/dL in subjects treated with evolocumab in the Japanese phase III study, suggesting the possibility that evolocumab may decrease LDL-C to a level not usually achieved by conventional therapies (a level below the range for which the benefit of LDL-C reduction was investigated in large-scale clinical studies). However, data on long-term safety of statins have been obtained from a very large number of patients, but not for evolocumab. Taking account of the above findings, the use of evolocumab should be limited to patients with high cardiovascular risk who require LDL-C reduction. The results of the Japanese phase III study conducted for this application demonstrated the significant efficacy and acceptable safety of evolocumab, when concomitantly administered with statins, in HC and HeFH patients with high cardiovascular risk. In Study 20110271, analyses for both the entire study population and the Japanese population showed the efficacy and safety of evolocumab in FH patients including HoFH patients. Therefore, these patient groups should be eligible for treatment with evolocumab. To identify patients with high cardiovascular risk, the risk should be assessed individually. Matters to be considered in risk assessment should be provided in an appropriate manner. Also, it is necessary to notify healthcare professionals in clinical settings of the fact that in the Japanese phase III study, not only patients with HC but also patients with other risk factors for cardiovascular events, such as history of ischemic heart disease, were included in the study. In order to appropriately include the above in the package insert, the specific description of the indications etc. will be finalized, also taking account of comments raised in the Expert Discussion.

4.(iii).B.(3) Efficacy

4.(iii).B.(3).1) Appropriateness of the primary endpoint

The primary objective for the treatment of HC is reduction of cardiovascular events, whereas no clinical data on cardiovascular risk reduction were submitted in this application. Therefore, PMDA asked the applicant to explain the appropriateness of the percent change in LDL-C level used as the primary efficacy endpoint in the confirmatory studies of evolocumab.

The applicant's explanation:

Data on epidemiologic studies show that, in diverse patient populations, LDL-C is a strong independent predictive factor for the risk of coronary artery disease. Also, a clinical study of statins provided the evidence that LDL-C reduction is beneficial to the cardiovascular system (Baigent C et al. *Lancet.* 2010;376:1670-1681). In the IMPROVE-IT study which compared the cardiovascular risk between simvastatin monotherapy and combination therapy with simvastatin and ezetimibe in patients with acute coronary syndrome, the mean LDL-C level at 1 year was 69.9 mg/dL in the monotherapy group and 53.2 mg/dL in the combination therapy group. The incidence of the primary composite endpoint (cardiovascular death, major coronary event, nonfatal stroke) at 7 years was 34.7% in the monotherapy group and 32.7% in the combination therapy group, showing a significant decrease in the combination therapy group (Cannon CP et al. *N Eng J Med.* 2015;372:2387-2397). Thus, LDL-C reduction yields clinical benefits; the greater the LDL-C reduction, the greater the clinical benefit. Therefore, the applicant considers that the LDL-C-lowering effect of evolocumab is of clinical significance.

PMDA's view:

A relationship between LDL-C and cardiovascular events has been investigated in multiple studies and their correlation has been demonstrated. Most of the evidence on the benefit of LDL-C reduction in the cardiovascular system has been obtained from clinical studies of statins. Regarding drugs other than statins, the cardiovascular risk-reduction effect of ezetimibe has been demonstrated in the IMPROVE-IT study. As for long-term study data, the incidence of cardiovascular events during the SoC-controlled period in Study 20120138 was 0.8% (15 of 1951 subjects) in the evolocumab group and 0.8% (8 of 977 subjects) in the control group. Also, the incidences of death, myocardial infarction, coronary revascularization, and cerebrovascular events in the evolocumab group were similar to those in the control group. According to the literature which included the above study (Marc S et al. *N Eng J Med.* 2015;372:1500-1509), 1-year cumulative incidence of the composite endpoint (death, myocardial infarction, hospitalization due to angina unstable, coronary revascularization, stroke, hospitalization due to transient cerebral ischemic attack or cardiac failure) in the OSLER-1 and 2 studies was 0.95% in the evolocumab group and 2.18% in the control group (Kaplan-Meier method). Thus, although currently available data did not directly confirm the cardiovascular risk-reduction effect of evolocumab compared with the comparator, they do suggest that lowering LDL-C level, by statins or by any other means, contributes to reduction of cardiovascular events. Also, currently available data from long-term studies do not suggest any increase in adverse events in the evolocumab group compared with the control group. Therefore, at present, the efficacy of evolocumab has been demonstrated in terms of LDL-C lowering. Long-term effects of evolocumab, including the duration of LDL-C-lowering effect and cardiovascular risk-reduction effect, remain to be investigated in the future. In order to investigate the effect of evolocumab on the incidence of cardiovascular events in routine clinical use in Japan, information should be collected appropriately via post-marketing surveillance, etc. The FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) study in patients with cardiovascular disease is currently ongoing to evaluate whether evolocumab in combination with statins prevent the relapse of cardiovascular events. Close attention should be paid to the results of the study.

4.(iii).B.(3).2) Efficacy in HC and HeFH patients

In the Japanese phase III study, HC and HeFH patients received evolocumab in combination with a statin. An analysis of the percent change from baseline in LDL-C at Weeks 10 and 12 showed a statistically significant reduction in LDL-C in all evolocumab dose groups compared with the placebo group. Table 38 shows the mean percent change from baseline in LDL-C (ultracentrifugation) at Weeks 10 and 12 in 24 HeFH patients enrolled in the Japanese phase III study (n = 7 in the evolocumab 140 mg Q2W group, n = 6 in the evolocumab 420 mg Q4W group, n = 6 in the placebo Q2W group, and n

= 5 in the placebo Q4W group). The percent change in LDL-C in HeFH patients was similar to that in HC patients.

Table 38. Mean percent change from baseline in LDL-C (ultracentrifugation) at Weeks 10 and 12 in HeFH patients enrolled in phase III study (FAS)

	Q2W		Q4W	
	Placebo	140 mg	Placebo	420 mg
Combination with atorvastatin 5 mg				
Number of subjects	3	3	2	3
Mean ± SD (%)	3.19 ± 18.52	−70.34 ± 17.92	13.41 ± 11.60	−69.04 ± 8.19
Combination with atorvastatin 20 mg				
Number of subjects	3	4	3	3
Mean ± SD (%)	−11.51 ± 11.87	−75.89 ± 8.78	1.31 ± 7.16	−82.16 ± 4.87

Based on the above results, PMDA considers as follows:
In the Japanese phase III study, evolocumab was shown to be superior to placebo in terms of the percent change from baseline in LDL-C at Weeks 10 and 12 (the primary endpoint). LDL-C at Weeks 10 and 12 in the evolocumab group was far below the target LDL-C level defined in the Japanese guidelines on arteriosclerosis. These findings have demonstrated the LDL-C-lowering effect of evolocumab in Japanese HC and HeFH patients.

4.(iii).B.(3).3) Effects on lipid parameters other than LDL-C

The applicant's explanation on the effect of evolocumab on lipid parameters other than LDL-C:
In the Japanese phase III study, the effects of evolocumab on non-HDL-C, apolipoprotein B (ApoB), TC, TC/HDL-C ratio, ApoB/apolipoprotein A-1 (ApoA1) ratio, TG, and HDL-C was investigated in addition to that on LDL-C. Evolocumab reduced non-HDL-C, ApoB, TC, TC/HDL-C ratio, ApoB/ApoA1 ratio, and TG and increased HDL-C, compared with baseline levels. The reduced or increased levels were maintained in Study 20120138, the extended part of the Japanese phase III study. After administration of evolocumab, non-HDL-C reached the level recommended by the guidelines on arteriosclerosis, and ApoB also decreased to the level recommended by the International Atherosclerosis Society (Bays HE et al. *J Clin Lipidol.* 2014;8:S1-S36.).

PMDA's view:
The efficacy of evolocumab in HC patients should be evaluated with the primary emphasis on LDL-C-lowering effect. However, it is also important to investigate whether or not evolocumab has adverse effects on other lipid parameters such as HDL-C and TG. In the Japanese phase III study, the mean TC, TG, non-HDL-C, ApoB, TC/HDL-C ratio, and ApoB/ApoA1 ratio decreased while HDL-C increased in the evolocumab group. Therefore, evolocumab does not have any adverse effect on at least these parameters.

4.(iii).B.(3).4) Efficacy in HoFH patients

The applicant's explanation on the efficacy in HoFH patients:
The efficacy of evolocumab was evaluated in Study 20110233 in non-Japanese HoFH patients and in Study 20110271 in HoFH patients and severe FH patients. There were no significant differences between Japanese and non-Japanese subjects in terms of extrinsic ethnic factors that would possibly affect the efficacy or safety of evolocumab. Since Study 20110121 showed that the PK and PD of evolocumab were similar between Japanese and Caucasian subjects receiving a single dose of evolocumab, intrinsic ethnic factors were also considered similar. Therefore, evaluation was performed on data including those obtained in foreign clinical studies. In Study 20110233, evolocumab 420 mg or placebo was administered Q4W for 12 weeks. The percent change (least squares mean ± SE) from baseline in LDL-C (ultracentrifugation) at Week 12, the primary endpoint, was −23.05% ± 3.78% in the evolocumab group and 7.88% ± 5.26% in the placebo group, showing a statistically significant reduction in LDL-C in the evolocumab group compared with the placebo group. In Study 20110271, evolocumab 420 mg was administered Q4W or Q2W to 100 HoFH patients. The percent change from baseline in LDL-C (ultracentrifugation) at Week 12 was −20.93% ± 23.96% (mean ± SD).

The efficacy of evolocumab in Japanese HoFH patients was assessed. Seven Japanese HoFH patients were evaluated in Study 20110271, and 5 of them were on apheresis at the enrollment. The percent change (mean ± SD) from baseline in LDL-C (ultracentrifugation) in the 7 Japanese subjects was −44.67% ± 35.02% at Week 12, −46.52% ± 31.31% at Week 24, and −61.03% ± 5.36% at Week 36, and that in the entire study population (100 subjects) was −20.93% ± 23.96% at Week 12, −23.35% ± 28.76% at Week 24, and −23.79% ± 26.74% at Week 36. After the start of treatment with evolocumab, 2 of 5 Japanese subjects on apheresis were able to discontinue apheresis by Week 4 of the extension study.

Japanese HoFH subjects showed a greater percent reduction in LDL-C compared with the entire study population. In HoFH patients, the extent of the loss of LDLR function varies depending on the mutation of the alleles for LDLR. One of the alleles was normal in 4 of 7 Japanese subjects, resulting in a difference in the distribution of genotype between the Japanese population and the entire study population. Among Japanese subjects, those with autosomal recessive hypercholesterolemia (homozygotes of LDLRAP1 mutation) did not show LDL-C reduction at Week 24. Genotypes of LDLR alleles potentially affect the efficacy of evolocumab, but genotyping is not easy and a relationship between genotype and LDLR activity inhibition is unclear. In addition, LDL-C reduction occurs rapidly after dosing of evolocumab. Therefore, identification of genotypes is not necessary before dosing of evolocumab. Instead, it will suffice to evaluate the efficacy after dosing of evolocumab.

PMDA's view:
Given the current status of treatment of HC, evolocumab has significance as one of new therapeutic options for FH patients, particularly for HoFH patients. Although evaluation data on HoFH patients are limited, the efficacy of evolocumab was demonstrated in Study 20110233 in non-Japanese HoFH patients. The efficacy of evolocumab was demonstrated in Study 20110271 as well, and data obtained from the Japanese subpopulation of HoFH patients suggest the efficacy of evolocumab. The applicant proposed that evolocumab is administered without identification of genotypes and then the patient's response to evolocumab therapy is evaluated to determine the usefulness of the therapy and the necessity of continued treatment in individual patients. PMDA considers the applicant's proposal for the following reasons: (i) There are no serious concerns about the safety of evolocumab at present, (ii) the LDL-C-lowering effect of evolocumab acting relatively immediately after dosing allows the efficacy to be evaluated within a short period, and (iii) the significance of determining the genotype of HoFH patients before dosing of evolocumab is not necessarily clear at present. However, expected LDL-C lowering is not achieved in some patients treated with evolocumab. This information should be communicated to healthcare professionals in clinical settings. The dosage and administration in HoFH patients will be further discussed in "4.(iii).B.(4) Dosage and administration."

4.(iii).B.(3).5) Efficacy in long-term treatment
The applicant's explanation on the long-term efficacy of evolocumab:
In the Japanese population of HC patients including HeFH patients in Study 20110110, the mean LDL-C level decreased by approximately 55% to 70% after dosing of evolocumab relative to baseline, and the decreased LDL-C persisted during the extended treatment period (≥64 weeks). An analysis of results in the Japanese population in Study 20120138 also showed LDL-C at Week 48 decreased by 65% to 75% in subjects treated with evolocumab plus the standard of care, compared to that at screening in the parent study. In this study, the percent reduction in LDL-C was similar between the evolocumab 140 mg Q2W group (100 subjects) and the evolocumab 420 mg Q4W group (110 subjects). In Study 20110271, the percent change (reduction) in LDL-C (ultracentrifugation) in 2 subjects treated with evolocumab for up to 48 weeks was −31.86% and −50.28%. The applicant considers that the above results demonstrate the long-term efficacy of evolocumab in Japanese HC and FH patients.

PMDA's view:
The LDL-C reduction was maintained during the long-term extension study of evolocumab, suggesting the long-term efficacy of evolocumab. However, the long-term clinical data were obtained from a small number of subjects during a limited treatment period. In particular, there are only limited data on long-term treatment with evolocumab 140 mg Q2W and on the use of evolocumab in HoFH patients. Therefore, relevant data should continue to be collected via post-marketing surveillance, etc.

4.(iii).B.(4) Dosage and administration

4.(iii).B.(4).1) Dosage and administration in HC and HeFH patients

The applicant's explanation on the appropriateness of the proposed dosage and administration in HC and HeFH patients:

In the Japanese phase II study, subjects received evolocumab (70 mg, 140 mg) or placebo Q2W, or evolocumab (280 mg, 420 mg) or placebo Q4W, for 12 weeks. The percent change from baseline in LDL-C (ultracentrifugation) at Week 12 was significantly different in all evolocumab groups compared with the placebo group. The percent change (least squares mean) relative to the placebo group was −52.85% in the 70 mg Q2W group, −68.61% in the 140 mg Q2W group, −58.16% in the 280 mg Q4W group, and −63.94% in the 420 mg Q4W group. The results revealed a greater efficacy in the 140 mg group (among Q2W regimens) and in the 420 mg group (among Q4W regimens). Since no clear relationship was observed between the dose of evolocumab and the incidence of adverse events, the dosage regimens of 140 mg Q2W and 420 mg Q4W were evaluated in the Japanese phase III study.

In the Japanese phase III study, evolocumab 140 mg Q2W, 420 mg Q4W, or placebo was administered for 12 weeks in combination with atorvastatin 5 or 20 mg/day given as the basal therapy. A significant difference was observed between all evolocumab groups and the placebo group in the mean percent change from baseline in LDL-C (ultracentrifugation) at Weeks 10 and 12, and other lipid parameters also showed improvement. The incidence of adverse events did not show any significant difference between the evolocumab 140 mg Q2W group and the 420 mg Q4W group. In the Japanese subjects who completed the Japanese phase II or III study and proceeded to the long-term extension study, LDL-C levels remained decreased. Based on the above results, the proposed dosage and administration for HC and HeFH patients was "The usual adult dosage of evolocumab is 140 mg once every 2 weeks or 420 mg once every 4 weeks, administered as a subcutaneous injection." Since comparable efficacy and safety are expected from both dosage regimens, the dosage regimen may be selected in a flexible manner by considering the convenience for the patient and other factors.

PMDA's view:

In HC and HeFH patients in the Japanese phase III study, a significant difference was observed in the percent change in LDL-C both between the evolocumab 140 mg Q2W group and the placebo group and between the 420 mg Q4W group and the placebo group, and the extent of the reduction in LDL-C did not differ significantly between the 140 mg Q2W group and the 420 mg Q4W group. It is therefore acceptable to make these dosage regimens of evolocumab available in clinical settings. The applicant does not propose any clear guide for selecting one regimen from the two, and assumes that the regimen is determined for individual patients. Since the results of clinical studies suggest similar efficacy and safety with both dosage regimens, it is appropriate, at present, to select either of the regimens depending on the convenience of hospital visit, etc.

4.(iii).B.(4).2) Dosage and administration in HoFH patients

The applicant's explanation on the dosage and administration in HoFH patients:

In Study 20110233 in non-Japanese HoFH patients, the percent reduction from baseline in LDL-C (by calculation or ultracentrifugation) at Week 12 was significantly greater in the evolocumab 420 mg Q4W group than in the placebo group. In Study 20110271 in HoFH patients and severe FH patients, the initial dose was evolocumab 420 mg Q4W for non-apheresis patients and 420 mg Q2W for apheresis patients, and the dose was to be increased to 420 mg Q2W, or decreased to 420 mg Q4W, using the percent reduction in LDL-C (≥5% or <5%) as the index (the trough concentration of PCSK9 [≥100 ng/mL or <100 ng/mL] was also used as an additional index in subjects who started with 420 mg Q4W). As it turned out, there were no subjects in whom up-titration was decided based on PCSK9 concentrations; up-titration was decided based on LDL-C levels and upon the physician's discretion. The dose was up-titrated to 420 mg Q2W in 43 (including 41 HoFH patients) of 192 non-apheresis patients (including 66 HoFH patients), and was down-titrated to 420 mg Q4W in 6 (including 5 HoFH patients) of 50 apheresis patients (including 34 HoFH patients). In Study 20110271 conducted with the above-described dosage regimens, LDL-C levels in the entire study population decreased from baseline, and the safety profile was not significantly different from that in HC and HeFH patients. Based on the above results, the applicant proposed the following dosage and administration for HoFH patients: "The usual dosage of evolocumab is 420 mg once every 4 weeks administered as a subcutaneous injection. Evolocumab 420 mg can be administered subcutaneously once every 2 weeks if an adequate response is not achieved."

The following description was included in the "Precautions for Dosage and Administration" section: "When used as an adjunct to LDL apheresis, evolocumab may be started at a dose of 420 mg once every 2 weeks and the same dose may be maintained."

PMDA asked the applicant to explain the appropriateness of including evolocumab 420 mg Q2W in the dosage and administration for HoFH patients.

The applicant's explanation:
In order to investigate the effect of the increased dose of evolocumab in non-apheresis patients who underwent up-titration in Study 20110271, an efficacy analysis was performed using the data from patients who received evolocumab 420 mg Q4W for ≥12 weeks followed by evolocumab 420 mg Q2W for ≥12 weeks. A total of 28 subjects met the criteria. All of the 28 subjects underwent up-titration at Week 12, and the mean percent change in LDL-C (ultracentrifugation) was −16.2% at Week 12 and −22.4% at Week 24, and the change in LDL-C was −56.7 at Week 12 and −81.4 mg/dL at Week 24, showing that up-titration resulted in increased efficacy. None of 3 non-apheresis Japanese patients (including 2 HoFH patients) underwent up-titration to 420 mg Q2W. Of 5 apheresis Japanese patients (all were HoFH patients), 3 continued 420 mg Q2W whereas 2 underwent down-titration to 420 mg Q4W or discontinued apheresis. Based on the above, the applicant considers that the LDL-C-lowering effect of the 420 mg Q2W regimen was superior to that of the 420 mg Q4W regimen in Study 20110271.

An analysis was made on the safety of the 420 mg Q2W regimen in HoFH patients in Study 20110271. The incidence of adverse events was 64.0% (16 of 25 subjects) with Q4W alone, 61.7% (29 of 47 subjects) with Q4W + Q2W (subjects who received both regimens in succession), and 82.1% (23 of 28 subjects) with Q2W alone. The incidence of serious adverse events was 0% with Q4W alone, 12.8% (6 of 47 subjects) with Q4W + Q2W (chest pain, aortic stenosis/coronary artery disease, coronary artery occlusion, non-cardiac chest pain, aortic valve disease, angina pectoris), and 14.3% (4 of 28 subjects) with Q2W alone (arteriovenous fistula, thrombosis, haematuria, carotid artery occlusion, myocardial ischaemia). On the other hand, the incidence of adverse events in severe FH patients was 56.5% (70 of 124 subjects) with Q4W alone, 66.7% (2 of 3 subjects) with Q4W + Q2W, and 53.3% (8 of 15 subjects) with Q2W alone. The incidence of serious adverse events was 0% with Q4W + Q2W, 1.6% (2 of 124 subjects) with Q4W alone (uterine prolapse, colitis), and 6.7% (1 of 15 subjects) with Q2W alone (angina pectoris). Adverse events in HoFH patients occurred more frequently in subjects treated with Q2W alone than in subjects treated with other regimens. However, the higher incidence of adverse events with Q2W alone is considered attributable to the following factors: (i) Most of subjects requiring treatment with the 420 mg Q2W regimen were on apheresis and therefore had a higher cardiovascular risk at enrollment compared with other subjects, (ii) adverse events in these patients were more likely to be reported because of the higher frequency of hospital visits, and (iii) the incidence of injection site reaction was higher because of the higher injection frequency. Therefore, the applicant does not consider that this result suggests an increased risk associated with the evolocumab 420 mg Q2W regimen. Observed injection site reactions were non-serious and did not necessitate dose reduction or treatment discontinuation in any subject.

Based on the above, the applicant considers that the evolocumab 420 mg Q2W regimen is useful both in apheresis patients and in non-apheresis patients on the 420 mg Q4W regimen for whom further LDL-C reduction is required, and that it is appropriate to add the 420 mg Q2W regimen to the dosage and administration for HoFH patients.

PMDA' view on the dosage and administration in HoFH patients:
The results of Study 20110233 and Study 20110271 have demonstrated the efficacy and safety of the 420 mg Q4W regimen in HoFH patients. In contrast, the evolocumab 420 mg Q2W regimen was investigated only in Study 20110271 in patients with HoFH and those with severe FH. Of 93 subjects who received evolocumab 420 mg Q2W (50 apheresis patients, 43 non-apheresis patients), 75 subjects (34 apheresis patients, 41 non-apheresis patients) were HoFH patients. It is therefore justifiable to add this dosage regimen to the dosage and administration for HoFH patients. In Study 20110271, the dose of evolocumab was to be adjusted according to LDL-C and PCSK9 concentrations, but dose up-titration was thought to have been decided based on the efficacy. Taking account of the above and the facts that the monitoring of PCSK9 concentrations is difficult in routine clinical practice and that the

appropriateness of the evolocumab dosage regimen decided based on PCSK9 concentrations is unclear, it is also justifiable to use the 420 mg Q2W regimen in patients with an inadequate response to 420 mg Q4W as assessed according to LDL-C. All of the apheresis patients started treatment with 420 mg Q2W and achieved reduction in LDL-C levels, with none of them requiring down-titration due to safety problem. Therefore, the starting dose of 420 mg Q2W in apheresis patients is acceptable. Thus, the dosage and administration proposed by the applicant are justified. On the other hand, physicians should not select the 420 mg Q2W regimen without careful consideration or continue to use the higher dose in non-responsive patients injudiciously because (i) the efficacy and safety of evolocumab 420 mg Q2W and Q4W were not compared in a randomized controlled manner and (ii) the incidence of injection site reaction, etc. was slightly higher with the 420 mg Q2W regimen. Whether the desired LDL-C-lowering effect is obtained by the selected dosage regimen should also be assessed. Information on the efficacy and safety of evolocumab 420 mg Q2W in HoFH patients should be collected via post-marketing surveillance, etc., and the obtained information should be provided promptly to healthcare professionals in clinical settings. Most of the HoFH patients evaluated in Japanese and foreign clinical studies were adults. The number of children aged <15 years who received evolocumab was 6 (1 aged 13 years, 5 aged 14 years [age at baseline]) in Study 20110233 and 8 (3 aged 13 years, 5 aged 14 years) in Study 20110271. All of them were non-Japanese children in a relatively high age group. Given the above situations, PMDA has to conclude that the currently recommended usual dosage and administration are intended for adult patients and that the dosage and administration recommended for pediatric patients as a whole remain unclear.

The dosage and administration should be modified as shown below, by taking account of the reviews in 4.(iii).B.(4).1) and 4.(iii).B.(4).2) above, but will be finalized, also taking account of comments raised in the Expert Discussion.

[Dosage and administration modified by PMDA]
Hypercholesterolemia and heterozygous familial hypercholesterolemia:
The usual adult dosage of Evolocumab (Genetical Recombination) is 140 mg once every 2 weeks or 420 mg once every 4 weeks, administered as a subcutaneous injection.

Homozygous familial hypercholesterolemia:
The usual adult dosage of Evolocumab (Genetical Recombination) is 420 mg once every 4 weeks administered as a subcutaneous injection. Evolocumab 420 mg can be administered subcutaneously once every 2 weeks if an adequate response is not achieved. When used as an adjunct to LDL apheresis, Evolocumab may be started at a dose of 420 mg once every 2 weeks.

(Underline denotes changes from the proposed dosage and administration.)

4.(iii).B.(5) Types of concomitant statins

In the Japanese phase III study, evolocumab was to be administered as an adjunct treatment for patients who were on atorvastatin 5 or 20 mg. Since atorvastatin was the only stain used concomitantly with evolocumab in the Japanese phase III study, PMDA asked the applicant to explain the efficacy and safety in patients who were treated with evolocumab in combination with statins other than atorvastatin.

The applicant's explanation:
Atorvastatin was concomitantly administered in the Japanese phase III study, whereas in the Japanese phase II study, concomitant use of various statins other than atorvastatin was allowed. Table 39 shows the percent change from baseline in LDL-C (ultracentrifugation) at Week 12, classified by concomitant statin mainly used in the Japanese phase II study. The results were similar among statins.

Table 39. Percent change from baseline in LDL-C (ultracentrifugation) at Week 12, classified by concomitant statin, in Japanese phase II study

	Pravastatin	Pitavastatin	Rosuvastatin	Atorvastatin
140 mg Q2W	−66.9 ± 15.4 (22)	−79.2 ± 9.7 (11)	−76.4 ± 7.9 (9)	−55.8 ± 9.6 (3)
420 mg Q4W	−59.4 ± 21.9 (26)	−66.4 ± 9.2 (6)	−69.3 ± 10.0 (10)	−69.8 ± 22.0 (6)

Mean ± SD (number of subjects)

An safety analysis was performed on adverse events reported in the 140 mg Q2W and 420 mg Q4W groups in the Japanese phase II study, classified by concomitant statin. The incidence of adverse events was 42.3% (41 of 97 subjects) with pravastatin, 46.4% (13 of 28 subjects) with pitavastatin, and 54.3% (25 of 46 subjects) with rosuvastatin. The pooled analysis of the Japanese phase II and III studies revealed that the incidence of adverse events in subjects receiving evolocumab 140 mg Q2W or 420 mg Q4W in combination with atorvastatin was 47.9% (105 of 219 subjects), thus showing no marked difference among subjects treated with different statins. The types and severity of observed events were also similar. In the foreign phase III study (Study 20110115) in which subjects were randomized to 5 statin cohorts (rosuvastatin 5 or 40 mg, atorvastatin 10 or 80 mg, simvastatin 40 mg), the efficacy and safety observed were similar among the statin cohorts. Based on the above, the efficacy and the safety of evolocumab are expected to be similar regardless of the types of concomitant statins.

PMDA's view:
As described above, the clinical positioning of evolocumab is an adjunct to statins [see "4.(iii).B.(1) Clinical positioning" and "4.(iii).B.(2) Indications"]. The Japanese phase III study and other studies also demonstrated the efficacy and safety of evolocumab in combination with atorvastatin. The efficacy and safety of evolocumab in combination with statins other than atorvastatin is expected to be similar to those of evolocumab plus atorvastatin, taking account of the data of the Japanese phase II study and foreign clinical studies.

4.(iii).B.(6) Safety[16)]

4.(iii).B.(6).1) Reduction of LDL-C to very low levels

Evolocumab has a potent serum LDL-C-lowering effect, inducing a LDL-C reduction to an extent not usually achieved by conventional therapies. Therefore, PMDA asked the applicant to explain possible risks caused by LDL-C reduction.

The applicant's response:
Given the LDL-C metabolism and cholesterol metabolism in major organs of humans, decreased serum LDL-C levels are unlikely to have any serious adverse effect. Also, in nonclinical studies of evolocumab, including the lifetime study in which serum LDL-C level was reduced to >10 mg/dL throughout the study period, no particular safety concerns were identified [see "3.(iii).A.(3).1) Carcinogenicity study in hamsters"]. The applicant therefore considers that very low serum LDL-C levels cause no safety problems.

In Japanese and foreign clinical studies of evolocumab, the safety was evaluated in subjects experiencing low LDL-C levels. Tables 40 and 41 show the incidence of adverse events reported in the placebo-controlled studies (Studies 20110231 and 20120122) enrolling Japanese subjects and in the Japanese population in the long-term extension studies. The safety profile in the subgroup of patients experiencing low levels of LDL-C was not substantially different from that in other subgroups. Only patients treated with evolocumab experienced LDL-C levels <40 mg/dL.

16) In this section, adverse events were tabulated using the data obtained at the following cut-off time point.
Study 20110110 and Study 20110271: [redacted]
Study 20120138: [redacted] (foreign countries), [redacted] (Japan)

Table 40. Adverse events in the evolocumab group in Japanese clinical studies, classified by serum LDL-C level

	<25 mg/dL[a]	<40 mg/dL[b]	≥40 mg/dL[c]
Number of subjects	247	348	59
Adverse events	48.2 (119)	47.4 (165)	55.9 (33)
Nasopharyngitis	19.4 (48)	17.8 (62)	18.6 (11)
Gastroenteritis	2.4 (6)	2.3 (8)	3.4 (2)
Bronchitis	2.0 (5)	1.4 (5)	0 (0)
Diabetes mellitus	2.0 (5)	2.0 (7)	0 (0)
Upper respiratory tract inflammation	2.0 (5)	2.3 (8)	0 (0)
Arthralgia	1.6 (4)	1.4 (5)	3.4 (2)
Blood CK increased	0.8 (2)	1.4 (5)	3.4 (2)
Abdominal pain upper	0.8 (2)	0.6 (2)	3.4 (2)
Myalgia	1.2 (3)	1.1 (4)	3.4 (2)
Serious adverse events	0.8 (2)	1.1 (4)	1.7 (1)

% (number of subjects)
The results of the pooled analysis of Study 20110231 and Study 20120122
a: Patients who had at least 1 post-baseline LDL-C value <25 mg/dL
b: Patients who had at least 1 post-baseline LDL-C value <40 mg/dL
c: Patients whose LDL-C remained ≥40 mg/dL after baseline

Table 41. Adverse events in the Japanese population (evolocumab group during the SoC-controlled period) in the long-term extension studies, classified by serum LDL-C level

	<25 mg/dL[a]	<40 mg/dL[b]	≥40 mg/dL[c]
Number of subjects	192	313	56
Adverse events	76.0 (146)	74.1 (232)	80.4 (45)
Nasopharyngitis	23.4 (45)	24.0 (75)	35.7 (20)
Diabetes mellitus	8.3 (16)	7.7 (24)	5.4 (3)
Bronchitis	4.2 (8)	4.5 (14)	7.1 (4)
Back pain	4.7 (9)	5.1 (16)	7.1 (4)
Headache	2.6 (5)	1.9 (6)	7.1 (4)
Serious adverse events	7.3 (14)	7.0 (22)	8.9 (5)

% (number of subjects)
The results of the combined analysis of data on Japanese subjects in Study 20110110 and Study 20120138
a: Patients who had at least 1 post-baseline LDL-C value <25 mg/dL
b: Patients who had at least 1 post-baseline LDL-C value <40 mg/dL
c: Patients whose LDL-C remained ≥40 mg/dL after baseline

In foreign clinical studies (including studies in patients without concomitant statins) as well, the safety profile in the subgroup of patients with low serum LDL-C levels was similar to that in other patient subgroups.

PMDA asked the applicant about the risk associated with evolocumab therapy, by referring to the reports on the relationship between low cholesterol levels and carcinogenicity (Gordon T et al. *Arch Intern Med.* 1981;141:1128-1131, Shepherd J et al. *Lancet.* 2002;360:1623-1630) and on the relationship between low cholesterol levels and cerebral haemorrhage (Iso H et al. *N Eng J Med.* 1989;320:904-910, Amarenco P et al. *N Eng J Med.* 2006;355:549-559).

The applicant's explanation:
In the carcinogenicity study in hamsters, there were no deaths or neoplastic or non-neoplastic changes related to evolocumab [see "3.(iii).A.(3).1) Carcinogenicity study in hamsters"]. In a prospective study which investigated the relationship between PCSK9 mutation and carcinogenicity in 13,250 subjects, the incidence of cancer was not higher in the subgroup of subjects with PCSK9 gene mutation than in the subgroup of those without PCSK9 gene mutation (Folsom AR et al. *Cancer Epidemiol Biomakers Prev.* 2007;16:2455-2458). In addition, large-scale epidemiological studies concluded that low serum cholesterol level does not increase carcinogenic risk (Baigent C et al. *Lancet.* 2005;366:1267-1278, Dale KM et al. *JAMA.* 2006;295:74-80, Alsheikh-Ali AA et al. *J Am Coll Cardiol.* 2008;52:1141-1147). Based on the above, the applicant considers that long-term use of evolocumab does not increase carcinogenic risk.

The findings on the relationship between low cholesterol level and haemorrhagic stroke were mainly based on limited data obtained in clinical studies. According to the recent meta-analysis, etc., no correlation was observed between LDL-C and hemorrhagic stroke (LaRosa JC et al. *Am J Cardiol.* 2013;111:1221-1229). Therefore, the applicant considers that evolocumab-induced LDL-C reduction does not increase the risk of hemorrhagic stroke.

Thus, no potential safety risk was identified that was associated with very low serum LDL-C levels, and clinical study data have demonstrated the favorable safety profile of evolocumab in subjects including those achieving very low LDL-C levels.

PMDA's view:
Among patients treated with evolocumab in clinical studies, some patients achieved very low serum LDL-C (<25 mg/dL), which is not usually seen with conventional therapies for HC. The effect of very low LDL-C levels has not been fully elucidated. In particular, the information on the long-term safety of evolocumab is still insufficient. On the other hand, there is currently no strong evidence for the risk of low LDL-C levels, taking account of the following facts: (i) There are currently no data suggesting an increased risk even in subjects achieving very low LDL-C levels in clinical studies, and (ii) potential risks associated with low LDL-C levels, induced by evolocumab or by any other means, have been discussed including the risk of carcinogenicity and cerebral haemorrhage, but none of them have been confirmed. Therefore, it is not necessary at present to take any measure such as preventing LDL-C levels from falling below a certain threshold in patients treated with evolocumab. The above discussion notwithstanding, given the important role of cholesterol in the body, information on the effect of very low LDL-C levels should continue to be collected. The relationship between LDL-C levels and the safety should continue to be evaluated in the post-marketing surveillance and, appropriate measures should be taken when new findings become available.

4.(iii).B.(6).2) Antibody production
The applicant's explanation on evolocumab-induced antibody production:
In the Japanese clinical studies (Studies 20110231 and 20120122) and in the Japanese population of the long-term extension studies (Studies 20110110 and 20120138), the incidence of anti-evolocumab antibodies in subjects receiving at least 1 dose of evolocumab was 0.4% (2 of 555 subjects). In addition, 2 subjects developed anti-evolocumab antibodies before dosing, resulting in a total of 4 Japanese subjects positive for anti-evolocumab antibodies. Even in these Japanese subjects positive for anti-evolocumab antibodies, LDL-C levels decreased by 31% to 84% from baseline at Week 12 to Week 52, demonstrating the efficacy of evolocumab. These 4 Japanese subjects did not experience any serious adverse event that was temporally related to the time when they yielded positive anti-evolocumab antibody test results, nor did they show hypersensitivity. No neutralizing antibodies were detected in any of these subjects. Serum evolocumab and unbound PCSK9 concentrations in the antibody-positive subjects were within the range of those in antibody-negative subjects in these studies. A pooled analysis of the Japanese and foreign clinical studies in PHMD patients[17)] (including studies in patients without concomitant statins) revealed that the incidence of anti-evolocumab antibodies in subjects receiving at least 1 dose of evolocumab was 0.3% (13 of 4915 subjects). No neutralizing antibodies were detected. Data from antibody-positive subjects did not suggest a lack of efficacy or safety problems. Because of the potential risk of antibody production in response to administration of protein preparations, information on the antibody production, efficacy, and safety will continue to be collected.

PMDA's view:
As discussed by the applicant, anti-evolocumab antibodies may be produced following administration of evolocumab. However, the incidence of anti-evolocumab antibodies was low in the Japanese and foreign clinical studies, and no neutralizing antibodies were detected. Also, data from anti-evolocumab antibody-positive subjects did not suggest major concerns about the efficacy or safety. Based on the above, no specific measures are necessary at present. However, the relationship between antibody production and the efficacy or safety was investigated in only a small number of subjects, and in an extremely small number of Japanese subjects in particular. Therefore, related information should be

17) Pooled analysis of foreign phase II studies (Studies 20090158, 20090159, 20101154, and 20101155), foreign phase III studies (Studies 20110109, 20110114, 20110115, 20110116, 20110117, 20120348, and 20120356), and a Japanese phase II study (Study 20110231)

collected in the post-marketing setting as well. The obtained information should be communicated to healthcare professionals as necessary.

4.(iii).B.(6).3) Injection site reaction

Since evolocumab is a solution for subcutaneous injection, PMDA asked the applicant to explain injection site-related adverse events.

The applicant's explanation:

A pooled analysis of Japanese clinical studies (Studies 20110231 and 20120122) showed that the incidence of injection site-related adverse events (events classified as "injection site reaction" in high level term [HLT] of MedDRA) was 2.0% (6 of 304 subjects) in the placebo group and 2.2% (9 of 407 subjects) in the evolocumab group. A pooled analysis of data from the Japanese populations during the SoC-controlled period of the long-term extension studies (Studies 20110110 and 20120138) showed the incidence of injection site-related adverse events was 2.7% (10 of 370 subjects) in the evolocumab group. Thus, all of the adverse events occurred less frequently and were Grade 1 or 2 in Common Terminology Criteria for Adverse Events (CTCAE). All the injection site reactions reported were classified as non-serious and did not result in study drug discontinuation in any of the subjects. No injection site reaction was observed in the Japanese population (n = 344) during the open-label period for the second year and onward (Year 2+ open-label period) of the extension studies. A pooled analysis of the Japanese and foreign clinical studies in PHMD patients[17] (including studies in patients without concomitant statins) revealed that the incidence of injection site reaction in the evolocumab group was as low as 2.4% to 4.1%. No serious adverse events were reported.

Based on the above, the applicant considers that evolocumab-associated injection site reaction is clinically acceptable.

PMDA's view:

The incidence of injection site reaction reported in clinical studies was not higher in the evolocumab group than in the control group. No serious adverse event reported. Taking account of the low severity of events reported and the absence of patients who discontinued the study, injection site reactions were considered of no clinical significance. However, in order to reduce the occurrence of injection site reaction-related adverse events, precautionary measures, such as changing the injection site for each dose, should be taken in the post-marketing setting, as done in clinical studies.

4.(iii).B.(6).4) Increased CK and muscle-related adverse events

The applicant's explanation:

In the clinical studies in Japanese subjects (Japanese clinical studies [Study 20110231, Study 20120122], the long-term extension studies [Study 20110110, Study 20120138]), no adverse events related to rhabdomyolysis or myopathy (events classified as Standardized MedDRA Queries [SMQ] "Rhabdomyolysis/myopathy [narrow search]") were reported. In Study 20110231, 1 subject in the evolocumab 70 mg Q2W group experienced increased CK and was diagnosed with myopathy. However, the increased CK had been noted before dosing of evolocumab, and resolved after discontinuation of ezetimibe while administration of evolocumab was continued. There were no other adverse events diagnosed as myopathy. Other muscle-related adverse events (events classified as SMQ "Rhabdomyolysis/myopathy [broad search]" in MedDRA) were identified by the pooled analysis of the Japanese clinical studies (Studies 20110231 and 20120122). Myalgia occurred in 0.3% (1 of 304) of subjects in the control group and 1.5% (6 of 407) of subjects in the evolocumab group. A pooled analysis of data from the Japanese populations in the long-term extension studies (Studies 20110110 and 20120138) revealed that myalgia occurred in 2.2% (4 of 176) of subjects in the control group and 2.4% (9 of 370) of subjects in the evolocumab group during the SoC-controlled period. A pooled analysis of the Japanese clinical studies (Studies 20110231 and 20120122) showed that CK level >5-fold the upper limit of normal (ULN) was noted in 0.7% (2 of 304) of subjects in the placebo group and 0.2% (1 of 407) of subjects in the evolocumab group. Among subjects with normal baseline CK, the incidence of CK elevation >5-fold the ULN was 0.4% (1 of 282 subjects) in the placebo group and 0.3% (1 of 359 subjects) in the evolocumab group. CK elevation >10-fold the ULN was not reported in the evolocumab group but was noted in 0.3% (1 of 304) of subjects in the control group. A pooled analysis of data from the Japanese populations in the long-term extension studies (Studies 20110110 and 20120138) showed

that CK level >5-fold the ULN was noted in 0.5% (2 of 370) of subjects in the evolocumab group at any post-baseline visit during the SoC-controlled period. A pooled analysis of the Japanese and foreign phase I studies (Studies 20080397, 20080398, 20110121, 20110168, 20120133, 20120136, and 20120341) showed that CK level >5-fold the ULN was noted in only 2.1% (11 of 521) of subjects in the evolocumab group at any post-baseline visit. In the evolocumab group of Study 20120133, rhabdomyolysis occurred at 56 days after the last dose of evolocumab, but its causal relationship to the study drug was ruled out. CK level >5-fold the ULN was not noted in HoFH patients evaluated in Part A of the foreign phase II/III study (Study 20110233), whereas in Part B, CK level >5-fold the ULN was noted in 6.3% (1 of 16) of subjects in the placebo group and 3.0% (1 of 33) of subjects in the evolocumab group, and CK elevation >10-fold the ULN was noted in 1 subject in the evolocumab group. In the long-term extension study (Study 20110271), CK elevation >10-fold the ULN was noted in 2 HoFH patients at Week 36 of the extension study. The CK elevation observed in both of these HoFH patients was related to physical exercise.

PMDA's view:
The CK elevation and muscle-related adverse events reported in the evolocumab group in the Japanese phase II and III studies are not necessarily attributable to evolocumab, because the incidences of those events were not clearly higher in the evolocumab group than in the control group and because all subjects used statins in these studies. However, given the CK elevation >5-fold the ULN in some subjects treated with evolocumab, attention should be paid to CK levels. Information on muscle-related adverse events and changes in CK levels should continue to be collected in the post-marketing setting.

4.(iii).B.(6).5) Effect on cognitive function and eyes
The literature reported that administration site reaction, myalgia, neurocognitive events, and ophthalmological events occurred more frequently in the subjects receiving alirocumab, a PCSK9 inhibitor that acts in a similar manner to evolocumab, than in those receiving placebo (Robinson JG et al. *N Engl J Med.* 2015;372:1489-1499). PMDA therefore asked the applicant to explain the effect of evolocumab on cognitive function and eyes.

The applicant's explanation on the effect on cognitive function:
Given the metabolism and biosynthesis of cholesterol in the brain, the homeostasis of cholesterol in the brain is unlikely to be affected by the serum LDL-C-lowering effect of evolocumab, suggesting that clinical use of evolocumab does not have impact on cognitive function [see "3.(i).B.(2).1) Possible effects of PCSK9 inhibition in tissues other than liver"]. Adverse events related to cognitive function (events classified as "deliria (incl confusion)," "cognitive and attention disorders and disturbances," "dementia and amnestic conditions," "disturbances in thinking and perception," or "mental impairment disorders" in the high-level group term [HLGT] of MedDRA) were not reported in the Japanese clinical studies (Studies 20110231 and 20120122). A pooled analysis of data from the Japanese populations in the long-term extension studies (Studies 20110110 and 20120138) showed that a cognitive function-related adverse event (perceptual disturbance of the lower lip) was noted in 0.3% (1 of 370) of subjects in the evolocumab group during the SoC-controlled period. The event was non-serious and its causal relationship to the study drug was ruled out. A pooled analysis of the Japanese and foreign clinical studies in PHMD patients[17] (including studies in patients without concomitant statins) showed that the incidence of cognitive function-related adverse events was 0.3% (6 of 2080 subjects) in the control group and 0.1% (5 of 3946 subjects) in the evolocumab group. The main adverse events reported were amnesia (0 and 2 subjects in the control and evolocumab groups, respectively) and disorientation (2 and 1 subjects, respectively). A pooled analysis of data from the entire population of the long-term extension studies (Studies 20110110 and 20120138) showed that the incidence of cognitive function-related adverse events reported during the SoC-controlled period was 0.2% (3 of 1489 subjects) in the control group and 0.8% (25 of 2976 subjects) in the evolocumab group. The main cognitive function-related adverse events were memory impairment (2 and 7 subjects in the control and evolocumab groups, respectively) and amnesia (1 and 7 subjects, respectively). Based on the above, the applicant considers that there are no safety concerns related to cognitive function.

Next, the applicant explained ophthalmologic events as follows:
No findings indicating ocular toxicity of evolocumab were observed in nonclinical studies. Eye-related adverse events (events classified as "Eye disorders" in the system organ class [SOC] of MedDRA)

reported in clinical studies were analyzed using the pooled data of the Japanese clinical studies (Studies 20110231 and 20120122). Eye-related adverse events occurred in 1.3% (4 of 304) of subjects in the placebo group (vitreous floaters [2 subjects], conjunctival haemorrhage and ocular hypertension [1 subject each]) and 1.0% (4 of 407) of subjects in the evolocumab group (asthenopia, conjunctival haemorrhage, keratitis, and vitreous floaters [1 subject each]). A pooled analysis of data from the Japanese populations in the long-term extension studies (Studies 20110110 and 20120138) showed that eye-related adverse events were noted in 3.8% (7 of 186) of subjects in the control group and 5.1% (19 of 370) of subjects in the evolocumab group during the SoC-controlled period. The main eye-related adverse events were cataract (4 and 1 subjects, respectively) and conjunctivitis allergic (0 and 2 subjects, respectively). During the Year 2+ open-label period, the incidence of eye-related adverse events was 0.6% (2 of 344 subjects, conjunctivitis allergic and photophobia [1 subject each]). A pooled analysis of the Japanese and foreign clinical studies in PHMD patients[17] (including studies in patients without concomitant statins) showed that eye-related adverse events were noted in 1.4% (30 of 2080) of subjects in the control group and 1.5% (60 of 3946) of subjects in the evolocumab group. The main eye-related adverse events were vision blurred (2 and 6 subjects in the control and evolocumab groups, respectively) and visual impairment (4 and 2 subjects, respectively). A pooled analysis of data from the entire populations of the long-term extension studies (Studies 20110110 and 20120138) showed that eye-related adverse events were noted in 2.4% (35 of 1489) of subjects in the control group and 3.0% (90 of 2976) of subjects in the evolocumab group during the SoC-controlled period. The main eye-related adverse events were cataract (14 and 26 subjects in the control and evolocumab groups, respectively), dry eye (1 and 12 subjects, respectively), conjunctivitis allergic (1 and 6 subjects, respectively), and vision blurred (1 and 5 subjects, respectively). Thus, no ophthalmological events raising safety concerns were identified, based on which the applicant considers that evolocumab does not cause any clinically relevant eye-related events.

PMDA' view on cognitive function-related adverse events noted after dosing of evolocumab:
During the SoC-controlled period in the long-term extension studies, the incidence of cognitive function-related adverse events was higher in the evolocumab group than in the control group, whereas the results of other clinical studies showed no consistent tendency toward a higher incidence in the evolocumab group than in the control group. Because of the small number of subjects and the short study period, the longer-term effect of evolocumab on the cognitive function is unclear. However, at present, there is no evidence requiring any specific tests to assess the cognitive function. Nevertheless, taking account of the applicant's discussions on the nonclinical studies and of the published literature, the possible long-term effect of evolocumab-induced low LDL-C levels on the brain cannot be excluded. The long-term safety of evolocumab should be evaluated in the post-marketing surveillance, etc.

Eye-related adverse events noted after dosing of evolocumab were analyzed. The results of Japanese and foreign clinical studies showed no tendency toward an increase in the incidence of these adverse events. At present, there are no data indicating the necessity of ophthalmological monitoring of patients. However, the long-term safety of evolocumab should be evaluated in the post-marketing surveillance, etc.

4.(iii).B.(6).6) Effect on hormones
Since evolocumab lowers cholesterol levels, PMDA asked the applicant to explain the effect of evolocumab on hormones.

The applicant's explanation:
During the SoC-controlled period of the long-term extension study (Study 20110110), adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), cortisol, testosterone, and estradiol levels were measured. Table 42 shows changes in hormone levels in the Japanese population classified by the lowest serum LDL-C level. No clinically meaningful changes were observed in any of the subgroups, showing no effect of LDL-C level on these hormones. Serum LDL-C levels <25 mg/dL were achieved only in the evolocumab group. The analysis for sex hormones (FSH, LH, testosterone, estradiol) excluded subjects receiving hormone replacement therapy, subjects who showed increased gonadotropin level at baseline (FSH ≥25 IU/L in women, LH ≥15 IU/L in men), and female subjects aged ≥50 years. Values at baseline, Weeks 12, 24, and 52 in 1 female subject included in the analysis (LDL-C ≥25 mg/dL) were as follows: FSH level was 6.6, 25.4, 12.4, and 5.8

IU/L, respectively; LH level was 5.7, 43.9, 3.3, and 13.1 IU/L, respectively; and estradiol level was 396.47, 763.57, 40.38, and 1666.63 pmol/L, respectively.

Table 42. Changes in hormone levels in the Japanese population, classified by serum LDL-C level (evolocumab group in Year 1 SoC-controlled period of long-term extension study [Study 20110110])

	Time point of measurement	<10 mg/dL	<25 mg/dL	≥25 mg/dL
ACTH (pmol/mL)	Baseline	3.4 ± 1.8 (5)	5.0 ± 2.8 (43)	5.3 ± 3.4 (67)
	Week 12	6.0 ± 6.8 (5)	6.0 ± 4.0 (50)	5.3 ± 2.7 (82)
	Week 24	4.9 ± 2.9 (5)	6.4 ± 3.7 (50)	5.6 ± 2.9 (81)
	Week 52	4.2 (1)	5.6 ± 2.6 (36)	5.3 ± 3.4 (62)
Cortisol (nmol/mL)	Baseline	317.95 ± 92.83 (5)	316.69 ± 98.52 (43)	318.64 ± 125.40 (67)
	Week 12	454.85 ± 198.45 (5)	325.90 ± 126.16 (50)	312.89 ± 106.24 (82)
	Week 24	372.05 ± 98.96 (5)	326.36 ± 112.86 (49)	319.50 ± 119.91 (80)
	Week 52	447.12 ± 139.20 (5)	324.96 ± 122.07 (50)	311.16 ± 123.49 (80)
FSH[a] (IU/L)	Baseline	5.2 ± 2.2 (5)	9.3 ± 6.0 (33)	10.3 ± 9.1 (35)
	Week 12	5.2 ± 3.2 (5)	9.2 ± 6.4 (33)	10.2 ± 9.4 (35)
	Week 24	4.8 ± 2.5 (5)	9.1 ± 6.4 (33)	9.4 ± 8.9 (34)
	Week 52	5.1 ± 3.1 (5)	9.2 ± 6.7 (33)	10.0 ± 9.2 (34)
LH[a] (IU/L)	Baseline	3.6 ± 1.7 (5)	5.5 ± 2.5 (33)	5.9 ± 2.7 (35)
	Week 12	3.9 ± 2.1 (5)	5.5 ± 2.8 (33)	5.8 ± 2.5 (35)
	Week 24	4.0 ± 2.0 (5)	5.6 ± 2.9 (33)	5.5 ± 2.9 (34)
	Week 52	3.8 ± 2.1 (5)	5.7 ± 3.4 (33)	5.9 ± 2.9 (34)
Testosterone [a] (nmol/L)	Baseline	13.998 ± 3.357 (5)	14.545 ± 4.084 (33)	17.143 ± 5.891 (35)
	Week 12	15.920 ± 3.454 (5)	17.708 ± 4.784 (33)	20.303 ± 6.933 (35)
	Week 24	15.455 ± 2.547 (5)	17.498 ± 4.498 (33)	19.189 ± 5.808 (34)
	Week 52	15.039 ± 2.451 (5)	17.479 ± 5.285 (33)	20.108 ± 6.438 (34)

Mean ± SD (number of subjects)
a: Male subjects

PMDA's view:
The data on hormone levels obtained in the long-term study were submitted by the applicant, albeit those from an extremely small number of subjects. The data showed no tendency suggestive of any clear effect of evolocumab within the dose range studied. Also, there was no tendency toward an increase in sex hormone-related adverse events in the evolocumab group [see "4.(iii).B.(6).1) Reduction of LDL-C to very low levels"]. Based on the above findings, no specific tests are necessary at present. However, the effect of evolocumab on hormones should be evaluated on a long-term basis through post-marketing surveillance, etc.

4.(iii).B.(6).7) Hepatic impairment

The applicant's explanation on evolocumab-induced hepatic impairment:
Evolocumab increases the hepatic uptake of circulating LDL by enhancing LDLR expression on the surface of hepatocytes. Theoretically, this mechanism will result in accumulation of cholesterol in hepatocytes, accompanied by an increase in the intracellular bile acid level, possibly causing hepatotoxicity. However, no particular hepatotoxicity was observed in the nonclinical studies.

Liver-related adverse events (events classified as "Drug related hepatic disorders - comprehensive search" in SMQ of MedDRA) reported in the clinical studies were analyzed. A pooled analysis of the Japanese clinical studies (Studies 20110231 and 20120122) showed that the incidence of liver-related adverse events was 2.2% (9 of 407 subjects) in the evolocumab group (alanine aminotransferase [ALT] increased [3 subjects], aspartate aminotransferase [AST] increased and liver function test abnormal [2 subjects each], and hepatic function abnormal, hepatic steatosis, urine bilirubin increased [1 subject each]; with some subjects experiencing more than 1 event) and 1.3% (4 of 304 subjects) in the placebo group (AST increased [2 subjects], hepatic function abnormal, hepatic steatosis, ALT increased, and blood bilirubin increased [1 subject each]; with some subjects experiencing more than 1 event). A pooled analysis of data from the Japanese populations in the long-term extension studies (Studies 20110110 and 20120138) showed that the incidence of liver-related adverse events reported during the SoC-controlled

period was 2.2% (8 of 370 subjects) in the evolocumab group (hepatic steatosis [4 subjects], hepatic function abnormal [3 subjects], ALT increased and AST increased [2 subjects each], liver injury and varices oesophageal [1 subject each]; with some subjects experiencing more than 1 event), and 1.1% (2 of 186 subjects) in the control group (hepatic cyst, hepatic function abnormal, ALT increased, AST increased, and gamma-glutamyltransferase increased [1 subject each]; with some subjects experiencing more than 1 event). No liver-related adverse events were reported during the Year 2+ open-label period.

Changes in hepatic enzyme levels were analyzed. A pooled analysis of the Japanese clinical studies (Studies 20110231 and 20120122) showed that ALT or AST >3-fold the ULN was noted in 0.7% (1 of 153) of subjects in the placebo Q2W group, 0.7% (1 of 151) of subjects in the placebo Q4W group, 0.7% (1 of 153) of subjects in the evolocumab 140 mg Q2W group, 0% (0 of 154) of subjects in the evolocumab 420 mg Q4W group, and 1.0% (1 of 100) of subjects in the evolocumab group with other dosage regimens. Neither ALT nor AST >5-fold the ULN was noted in any subjects studied. A pooled analysis of data from the Japanese populations in the long-term extension studies (Studies 20110110 and 20120138) showed that during the SoC-controlled period, AST >3-fold the ULN was noted in 1.1% (2 of 186) of subjects in the control group and 1.6% (6 of 370) of subjects in the evolocumab group, and AST >5-fold the ULN in 3 subjects in the evolocumab group.

A pooled analysis of the Japanese and foreign clinical studies in PHMD patients[17] (including studies in patients without concomitant statins) also showed the incidence of liver-related adverse events and the percentage of patients with abnormal hepatic enzyme levels were low, as were the cases with the Japanese population.

The Japanese and foreign phase II and III studies excluded subjects with active hepatic disease or hepatic impairment (AST or ALT >2-fold the ULN), and the safety in patients with severe hepatic impairment was not investigated. In the clinical pharmacology study (Study 20120341) which assessed the effect of hepatic impairment on the PK of evolocumab, subjects with normal hepatic function, subjects with mild hepatic impairment, and subjects with moderate hepatic impairment were evaluated (n = 8 per group). The incidence of adverse events was 12.5% (1 of 8 subjects) in the group of subjects with normal hepatic function (haemorrhoids), 50.0% (4 of 8 subjects) in the group of subjects with mild hepatic impairment (diarrhoea/vomiting/rash pruritic, headache, depression, breast mass), and 25.0% (2 of 8 subjects) in the group of subjects with moderate hepatic impairment (ascites/parotitis, diarrhoea/decreased appetite/rash pustular/urinary tract infection/tachycardia). A causal relationship to the study drug was ruled out for all adverse events observed, posing no safety concerns in subjects with mild to moderate hepatic impairment.

There were no liver-related safety problems in Japanese or foreign clinical studies.

PMDA's view:
Japanese and foreign clinical studies did not present data suggestive of any clinically relevant hepatic impairment induced by evolocumab. Nor was there any risk suggesting the necessity of restricting the use of evolocumab in subjects with hepatic impairment. On the other hand, patients with clinically relevant hepatic impairment or hepatic disease were not enrolled in the Japanese and foreign phase II and III studies as a general rule. This resulted in limited safety data obtained in this patient group. Post-marketing information on the effect of evolocumab on the liver should be collected.

4.(iii).B.(6).8) Diabetes mellitus and increase in blood glucose
The applicant's explanation on the risk of diabetes mellitus associated with evolocumab therapy:
The incidence of diabetes mellitus-related adverse events (events classified as "Hyperglycaemia/new onset diabetes mellitus [broad search]" in SMQ of MedDRA) was analyzed. A pooled analysis of the Japanese clinical studies (Studies 20110231 and 20120122) showed that the incidence of diabetes mellitus-related adverse events was 3.9% (12 of 304 subjects) in the placebo group (diabetes mellitus [7 subjects], type 2 diabetes mellitus [4 subjects], depressed level of consciousness and hypoglycaemia [1 subject each]; with some subjects experiencing more than 1 event) and 3.2% (13 of 407 subjects) in the evolocumab group (diabetes mellitus [7 subjects], blood glucose increased, glycosylated haemoglobin increased, diabetes mellitus inadequate control, type 2 diabetes mellitus, glucose tolerance impaired, hypoglycaemia, and dehydration [1 subject each]; with some subjects experiencing more than 1 event).

A pooled analysis of data from the Japanese populations in the long-term extension studies (Studies 20110110 and 20120138) showed that the incidence of diabetes mellitus-related adverse events was 6.5% (12 of 186 subjects) in the control group and 9.5% (35 of 370 subjects) in the evolocumab group for the events reported during the SoC-controlled period. These events were not noted in the Year 2+ open-label period. During Year 1 SoC-controlled period of the long-term extension studies, the incidence of diabetes mellitus-related adverse events was higher in the evolocumab group than in the control group. This was probably attributable to the higher percentage of subjects with a history of type 2 diabetes mellitus in the evolocumab group (47.6%, 175 of 368 subjects) compared with the control group (38.9%, 72 of 185 subjects).

Changes in fasting blood glucose and HbA1c levels from baseline are presented in Table 43, showing that both parameter values were similar between the treatment groups.

Table 43. Evolocumab-induced changes in fasting blood glucose and HbA1c levels from baseline in Japanese population

	Japanese clinical studies[a]		Long-term extension studies[b]		
			SoC-controlled period		Open-label period
	Placebo	Evolocumab	Control	Evolocumab	Evolocumab
Fasting blood glucose (mg/dL)					
Baseline value	114.6 ± 25.6 (n = 304)	114.8 ± 26.3 (n = 407)	114.6 ± 28.8 (n = 186)	115.0 ± 24.0 (n = 370)	113.0 ± 25.2 (n = 203)
Change at Week 12	2.2 ± 18.4 (n = 300)	1.1 ± 18.7 (n = 402)			
Week 24 in the extension study			−3.8 ± 19.5 (n = 184)	1.1 ± 19.3 (n = 369)	
Week 52 in the extension study			−0.9 ± 20.7 (n = 71)	1.4 ± 19.8 (n = 144)	
Week 64 in the extension study					1.8 ± 14.6 (n = 70)
HbA1c (%)					
Baseline value	6.20 ± 0.77 (n = 304)	6.19 ± 0.74 (n = 406)	6.14 ± 0.75 (n = 186)	6.23 ± 0.76 (n = 369)	6.20 ± 0.72 (n = 203)
Change at Week 12	0.16 ± 0.50 (n = 301)	0.08 ± 0.33 (n = 404)			
Week 24 in the extension study			0.03 ± 0.36 (n = 183)	0.07 ± 0.48 (n = 360)	
Week 52 in the extension study			−0.05 ± 0.33 (n = 71)	−0.03 ± 0.53 (n = 144)	
Week 64 in extension study					−0.10 ± 0.34 (n = 69)

Mean ± SD
a: Pooled data of Study 20110231 and Study 20120122
b: Pooled data of Study 20110110 and Study 20120138

A pooled analysis of foreign clinical studies in PHMD patients[17] (including studies in patients without concomitant statins) showed that the incidence of diabetes mellitus-related adverse events (broad search) was 1.5% (32 of 2080 subjects) in the control group and 1.6% (63 of 3946 subjects) in the evolocumab group. The main adverse events were diabetes mellitus (0.3% in the control group versus 0.3% in the evolocumab group) and type 2 diabetes mellitus (0.2% versus 0.2%). A pooled analysis of the entire populations of the long-term extension studies (Studies 20110110 and 20120138) showed that diabetes mellitus-related adverse events were noted in 3.3% (49 of 1489) of subjects in the control group and 2.9% (87 of 2976) of subjects in the evolocumab group for those reported during the SoC-controlled period. The main adverse events were diabetes mellitus (0.7% in the control group versus 1.0% in the evolocumab group) and type 2 diabetes mellitus (0.5% versus 0.7%). During the Year 2+ open-label period, diabetes mellitus-related adverse events were noted in 1.9% (32 of 1675) of subjects, and the main adverse events reported were type 2 diabetes mellitus (0.6%) and diabetes mellitus (0.4%). Changes in fasting blood glucose and in HbA1c levels were similar between treatment groups.

Based on the above findings, the applicant considers that evolocumab does not pose any clinically relevant risk of diabetes mellitus-related adverse events.

PMDA's view:
The incidence of diabetes mellitus-related adverse events was higher in the evolocumab group than in

the control group among the Japanese population during the SoC-controlled period of the long-term extension studies. The applicant explained that this difference may have been attributed to the difference in patient characteristics. The applicant's explanation is acceptable. Taking also account of changes in fasting blood glucose and HbA1c levels, at present, no clear risk of impaired glucose tolerance associated with evolocumab therapy is suggested by data. However, information on the effect of long-term use of evolocumab on glucose tolerance, etc. should continue to be collected via post-marketing surveillance, etc.

4.(iii).B.(6).9) Safety in patients with hepatitis C virus infection

The applicant's explanation on the use of evolocumab in patients with hepatitis C virus (HCV) infection:
LDLR has been reported to be involved in HCV entry into cells (Agnello V et al. *Proc Natl Acad Sci USA.* 1999;96:12766-12771). Another publication reported that HCV up-regulates the expression of cell-surface LDLR in the HCV-infected cells and modulates lipid metabolism, thereby promoting its replication (Albecka A et al. *Hepatology.* 2012;55:998-1007, Syed GH et al. *J Virol.* 2014;88:2519-2529). Thus, given the potential role of LDLR in HCV replication, it is theoretically conceivable that HCV infection of hepatic cells is enhanced by PCSK9 inhibition-induced increase in LDLR expression.

In Japanese phase II (Study 20110231) and phase III (Study 20120122) studies, a test for anti-HCV antibody was performed in patients at high risk of HCV infection due to a history of blood transfusion, etc., patients with a history of HCV infection, and patients with AST or ALT>2-fold the ULN. Of 20 Japanese patients tested, 3 were found to be positive. All the 3 patients had the liver function test (LFT) values >2-fold the ULN throughout the study period. Of the 3 patients, 1 had detectable HCV RNA at baseline and during the study period. In other 2 patients, HCV RNA was undetectable throughout the study period, and their LFT values remained consistent. In the phase I study in subjects with hepatic impairment (Study 20120341), all of 8 subjects with mild hepatic impairment and 4 of 8 subjects with moderate hepatic impairment had hepatitis C, but no safety concerns were identified in these subjects. In the foreign clinical study in PHMD patients, of 216 subjects who underwent a test for anti-HCV antibody, 9 were found to be positive. The LFT values in these anti-HCV antibody positive subjects, except one, were <2-fold the ULN at all measuring time points. The 1 subjects had AST and ALT levels >2-fold the ULN at screening, but all LFT values were within the normal range at baseline and after the start of administration. HCV RNA was detected in 2 of the 9 subjects at baseline or during the treatment period, whereas in the other 7 subjects, HCV RNA was below the detection limit with stable LFT values throughout the study period. In the long-term extension study (Study 20120138), HCV RNA was detected in another subject. This subject had not been tested for anti-HCV antibody. Thus, currently available data provide no evidence indicative of the relationship between evolocumab and aggravation of HCV infection. However, since only limited data were available for evaluation, further information will be collected.

PMDA's view:
Clinical study data do not suggest any significant safety problem in patients with HCV infection. It is therefore unnecessary at present to include HCV infection in the contraindications for the use of evolocumab. Theoretically, however, the possibility cannot be excluded that evolocumab may increase the risk of onset or aggravation of hepatitis C. Information should be collected via post-marketing surveillance, etc. If new safety problems are found, the obtained information should be communicated to healthcare professionals in clinical settings in an appropriate manner.

4.(iii).B.(6).10) Safety in long-term treatment

The applicant's explanation on the long-term safety of evolocumab:
Tables 44 and 45 show the incidences of adverse events (those reported by ≥5% of subjects in either of the HC patient groups) in the Japanese populations in the long-term extension studies (Studies 20110110 and 20120138).

Table 44. Incidence of adverse events in Study 20110110 (Japanese population)

	HeFH		HC	
	Evolocumab	Control	Evolocumab	Control
Number of subjects	3	10	143	63
All adverse events	100.0 (3)	80.0 (8)	82.5 (118)	79.4 (50)
Nasopharyngitis	0 (0)	40.0 (4)	33.6 (48)	38.1 (24)
Diabetes mellitus	0 (0)	0 (0)	9.1 (13)	4.8 (3)
Back pain	0 (0)	0 (0)	7.0 (10)	1.6 (1)
Periodontitis	0 (0)	0 (0)	6.3 (9)	0 (0)
Contusion	0 (0)	0 (0)	4.9 (7)	7.9 (5)
Cataract	0 (0)	0 (0)	0.7 (1)	6.3 (4)
Serious adverse events	0 (0)	0 (0)	9.8 (14)	7.9 (5)

% (number of subjects)

Table 45. Incidence of adverse events in Study 20120138 (Japanese population)

	HeFH		HC	
	140 mg Q2W	420 mg Q4W	140 mg Q2W	420 mg Q4W
Number of subjects	10	4	91	119
All adverse events	90.0 (9)	75.0 (3)	72.5 (66)	65.5 (78)
Nasopharyngitis	20.0 (2)	0 (0)	22.0 (20)	21.0 (25)
Bronchitis	0 (0)	25.0 (1)	5.5 (5)	6.7 (8)
Diabetes mellitus	0 (0)	0 (0)	3.3 (3)	9.2 (11)
Back pain	10.0 (1)	0 (0)	3.3 (3)	5.0 (6)
Influenza	0 (0)	0 (0)	1.1 (1)	5.0 (6)
Serious adverse events	0 (0)	0 (0)	6.6 (6)	5.9 (7)

% (number of subjects)

The incidences of serious adverse events and of adverse events leading to study drug discontinuation were low, showing no significant difference between the evolocumab and control groups. Diabetes mellitus and type 2 diabetes mellitus occurred slightly more frequently in the evolocumab group than in the control group, conceivably due to the greater number of patients with a history of diabetes mellitus in the evolocumab group than in the control group [see "4.(iii).B.(6).8) Diabetes mellitus and increase in blood glucose"]. The incidence of adverse events did not increase with the increasing duration of treatment. Among HC patients, the incidence of adverse events was similar between the 140 mg Q2W group and the 420 mg Q4W group. The incidence of adverse events in HeFH patients was not substantially different from that in HC patients although a meaningful comparison was practically impossible because of the small number of HeFH patients enrolled in both studies. The above results support the long-term safety of evolocumab in Japanese patients, and are consistent with those of the foreign clinical studies.

PMDA' view on the long-term safety of evolocumab:
The results of the long-term study in patients including Japanese patients did not show any increase in adverse events that would pose problems during long-term evolocumab therapy, neither did they detect any adverse event specific to long-term treatment. On the other hand, given the possibility that evolocumab may be used clinically over several decades, post-marketing information on the long-term safety of evolocumab should be collected because of the currently limited experience with long-term use.

4.(iii).B.(7) Self-injection

The applicant's explanation on the self-injection of evolocumab:
In the long-term extension study (Study 20120138), 86.5% (193 of 223 subjects) of Japanese subjects in the evolocumab group self-injected all doses, and 10.8% (24 of 223 subjects) self-injected a part of the doses. The safety data from Study 20120138 and the safety data from the Japanese phase II (Study 20110231) and phase III (Study 20120122) studies, in both of which evolocumab was administered to most of the patients by healthcare professionals, were evaluated by comparing adverse events, serious adverse events, and adverse events leading to study drug discontinuation. As a result, no new clinically significant adverse events were detected in subjects who self-injected evolocumab. Before the application of self-injection, its appropriateness will be carefully considered by the physician for each

patient, and the physician or other healthcare professionals will provide the patient with adequate education and training for self-injection. The patient will not be allowed to self-inject evolocumab unless the physician confirm that the patient can do so without failure. At the same time, the patient will be instructed to report to the medical institution if, after the start of self-injection, any adverse reaction to evolocumab is suspected or continued self-injection is difficult. In the event of adverse reactions or other abnormalities, the physician will promptly take appropriate measures, such as termination of self-injection. To ensure that these procedures are taken appropriately, the applicant will prepare information materials to be supplied to patients through physicians or other healthcare professionals.

PMDA's view:
In Japan, no self-injectable drugs for the treatment of dyslipidemia are approved at present. However, evolocumab is a solution for subcutaneous injection, and subcutaneous self-injection per se is not a novel administration technique because self-injectable drugs are already approved for the indication of other diseases. In the clinical studies in which evolocumab was administered by self-injection, no problematic events were noted. Based on the above, patients who have received appropriate training are allowed to self-inject evolocumab. Since adequate patient training is required for the control of the drug, injection technique, and disposal of the device, relevant information should be provided to healthcare professionals so that appropriate guidance can be given to patients.

4.(iii).B.(8) Post-marketing investigations
The applicant's explanation on post-marketing investigations:
A specified drug use-results survey will be conducted using the central registry system (observation period, 2 years; number of patients to be registered, 3000) in order to evaluate the long-term safety and efficacy of evolocumab in routine clinical use. This survey aims to collect information on the safety in pediatric patients, elderly patients (≥75 years old), patients with hepatic impairment (severe hepatic impairment with Child-Pugh class C in particular), and patients with HCV infection. The survey is also intended to evaluate hypersensitivity, immunogenicity, and the effect of low LDL-C levels (<40 mg/dL). Of the 3000 patients to be registered, approximately 300 will be patients with hepatic impairment (only limited data were obtained from this patient group in clinical studies) and another 300 will be elderly patients (≥75 years old). This will allow safety evaluation separately for patients with different characteristics.

PMDA's view:
The clinical studies of evolocumab were designed to evaluate patients with only a limited range of background characteristics, with a resultant limitation in data on patients with hepatic impairment and on elderly patients (≥75 years old). For this reason, post-marketing surveillance should be conducted to collect information such as the long-term safety and efficacy evolocumab, hypersensitivity, immunogenicity, the incidence of cardiovascular events, and the effect of low LDL-C level (<40 mg/dL) in patients, including these patient populations. The details of the post-marketing surveillance will be finalized, taking account of comments raised in the Expert Discussion, including the appropriateness of safety specifications and risk classification as well as the appropriateness of pharmacovigilance and risk minimization activities, according to "Risk Management Plan Guidance" (Notification issued jointly by the Safety Division, Pharmaceutical and Safety Bureau, MHLW [No. 0411-1] and the Evaluation and Licensing Division, Pharmaceutical and Safety Bureau, MHLW [No. 0411-2], dated April 11, 2012).

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

The assessment is currently ongoing. The results and PMDA's conclusion will be reported in the Review Report (2).

IV. Overall Evaluation

Based on the submitted data, the efficacy of evolocumab in the treatment of hypercholesterolemia (including familial hypercholesterolemia) has been demonstrated and its safety is acceptable in view of its observed benefits. The product provides a new therapeutic option for hypercholesterolemia, and thus

is of clinical significance. Also, further discussions are needed for the indication, dosage and administration, precautionary statements in the package insert, and post-marketing investigations.

This application may be approved if evolocumab is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

November 4, 2015

I. Product Submitted for Registration

[Brand name]	(a) Repatha SC Injection 140 mg Syringe (b) Repatha SC Injection 140 mg Pen
[Non-proprietary name]	Evolocumab (Genetical Recombination)
[Applicant]	Amgen Astellas BioPharma K.K.
[Date of application]	March 20, 2015

II. Content of the Review

The comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1. Clinical positioning of evolocumab

In the Japanese and foreign guidelines, HMG-CoA reductase inhibitors (statins) are positioned as the first-line drug therapy in patients with hypercholesterolemia (HC). The results of the Japanese phase III study confirmed the low-density lipoprotein cholesterol (LDL-C)-lowering effect and the safety of Repatha SC Injection 140 mg Syringe and Repatha SC Injection 140 mg Pen (hereinafter referred collectively to as "Repatha" or "evolocumab") used as an adjunct to statins in HC patients with high cardiovascular risk. Based on the above, PMDA has concluded that evolocumab should be administered in combination with conventional therapies including statins to HC patients with high cardiovascular risk who have had an inadequate response to statin therapy. This conclusion was supported by the expert advisors.

2. Indications

PMDA has concluded from the clinical positioning of evolocumab that the drug should be used at least in HC patients who have had an inadequate response to conventional therapies including statins. PMDA has also concluded that use of evolocumab should be limited to HC patients with high cardiovascular risk who are in high need of lowering LDL-C. These conclusions of PMDA were supported by the expert advisors. Furthermore, PMDA concluded from the results of the Japanese phase III study and Study 20110271 that evolocumab should be indicated for the treatment of patients with heterozygous familial hypercholesterolemia (HeFH) and patients with homozygous familial hypercholesterolemia (HoFH). This conclusion was also supported by the expert advisors. In addition, the following comments were raised by the expert advisors:

- Taking account of the facts that (1) the cardiovascular risk-reduction effect of evolocumab has not been confirmed currently and (2) evolocumab acts by a novel mechanism and its long-term safety has not been fully demonstrated, patients with familial hypercholesterolemia (FH) should be the first to be treated with evolocumab, followed by HC patients for the secondary prevention of recurrence of atherosclerotic diseases.
- Due consideration should be given to the use of evolocumab in HC patients with high cardiovascular risk who require the primary prevention of cardiovascular events. For example, evolocumab should not be administered indiscriminatingly to patients with diabetes mellitus on statins who have LDL-C >100 mg/dL. Instead, evolocumab should be administered to patients who are considered to be at high risk of cardiovascular events, with consideration given to complications, history of diseases and other factors.

Based on the above discussions, PMDA has concluded that injudicious use of evolocumab should be avoided, and that physicians should be advised to confirm that candidate patients have high

cardiovascular risk before determining their eligibility for evolocumab therapy. For this purpose, the following "Indications," "Precautions for Indications," and "Precautions for Dosage and Administration" should be included in the package insert:

[Indications]
Familial hypercholesterolemia, hypercholesterolemia
The product should be used only in patients with high cardiovascular risk who have had an inadequate response to HMG-CoA reductase inhibitors.

[Precautions for Indications]
1. Detailed tests should be performed to confirm a diagnosis of familial hypercholesterolemia or hypercholesterolemia. Use of evolocumab should be considered only for the patient with a definite diagnosis of either of the above diseases.
2. Physicians should confirm that patients with non-familial hypercholesterolemia have high cardiovascular risk by examining the current or past comorbid conditions including coronary artery disease, non-cardiogenic cerebral infarction, peripheral arterial disease, diabetes mellitus, and chronic kidney disease, and thereby determine the eligibility of each patient for evolocumab therapy [see the "Clinical Studies" section].

[Precautions for Dosage and Administration]
Evolocumab should be administered in combination with an HMG-CoA reductase inhibitor.
(The efficacy and safety of evolocumab as monotherapy has not been established in Japanese patients.)

3. Efficacy

(1) Appropriateness of the primary endpoint

Although there is currently no direct evidence to support the cardiovascular risk-reduction effect of evolocumab, LDL-C lowering induced by statins or other lipid lowering therapies has been reported to contribute to the reduction of cardiovascular events. There have been no significant concerns raised about the long-term safety of evolocumab. Taking account of these facts, PMDA has concluded that the efficacy of evolocumab has been demonstrated by its LDL-C-lowering effect and that evolocumab is recommended for clinical use. PMDA has also concluded that the post-marketing surveillance and other programs should be conducted to appropriately collect information on the effect of evolocumab on the incidence of cardiovascular events in routine clinical use in Japan. The above conclusions of PMDA were supported by the expert advisors.

(2) Efficacy in HoFH patients

Although evaluation data on HoFH patients are limited, PMDA has concluded that evolocumab is expected to be effective in this patient group, on the basis of the results of the foreign Study 20110233 and the Global Study 20110271 in HoFH patients. The conclusion of PMDA was supported by the expert advisors. Depending on the genotype of LDL receptor, some HoFH patients may not respond to evolocumab. However, the LDL-C-lowering effect of evolocumab can be evaluated relatively quickly and there are no significant safety concerns associated with evolocumab therapy. Therefore, PMDA has concluded that the following procedure is acceptable: Evolocumab is administered without identification of the genotype of LDL receptor, and then the patient's response to evolocumab therapy is evaluated to determine the usefulness of evolocumab and the necessity of continued treatment in individual patients. This conclusion of PMDA was supported by the expert advisors.

4. Dosage and administration

(1) Dosage and administration in HC patients and HeFH patients

The Japanese phase III study demonstrated the efficacy of evolocumab 140 mg once every 2 weeks (Q2W) and 420 mg once every 4 weeks (Q4W), and the extent of LDL-C reduction was not significantly different between the 2 groups. Based on the above, PMDA has concluded that these 2 dosage regimens are made available in clinical settings and one of the regimens can be selected according to the patient's convenience of hospital visit, etc. The conclusion of PMDA was supported by the expert advisors.

(2) Dosage and administration in HoFH patients

The efficacy and safety of evolocumab 420 mg Q4W in HoFH patients were demonstrated in Studies 20110233 and 20110271. The efficacy and safety of evolocumab 420 mg Q2W were also evaluated in Study 20110271, in which most of the patients receiving 420 mg Q2W were HoFH patients. Based on the above results, PMDA has concluded that 420 mg Q4W is the recommended dosage regimen for HoFH patients and up-titration to 420 mg Q2W is allowed in patients who have an inadequate response to the 420 mg Q4W regimen. PMDA has also concluded from the results of Study 20110271 that an initial dose of 420 mg Q2W may be considered in patients on apheresis. These conclusions of PMDA were supported by the expert advisors.

Because of the scanty data on the use of evolocumab in pediatric patients, PMDA has concluded that, at present, the recommended usual dosage and administration are intended for adult patients and that the dosage and administration recommended for pediatric patients as a whole remain unclear. The conclusion of PMDA was supported by the expert advisors.

Based on (1) and (2) above, PMDA has concluded that the dosage and administration should be as follows:

[Dosage and administration]
Heterozygous familial hypercholesterolemia and hypercholesterolemia:
The usual adult dosage of Evolocumab (Genetical Recombination) is 140 mg once every 2 weeks or 420 mg once every 4 weeks, administered as a subcutaneous injection.

Homozygous familial hypercholesterolemia:
The usual adult dosage of Evolocumab (Genetical Recombination) is 420 mg once every 4 weeks administered as a subcutaneous injection. Evolocumab 420 mg can be administered subcutaneously once every 2 weeks if an adequate response is not achieved. When used as an adjunct to LDL apheresis, Evolocumab may be started at a dose of 420 mg once every 2 weeks subcutaneously.

5. Safety

At present, no clinically significant problems have been suggested regarding events potentially associated with treatment with evolocumab, such as reduction of LDL-C to very low levels, antibody production, injection site reaction, increased blood creatine phosphokinase and muscle-related adverse events, effect on cognitive function, effect on the eyes, effect on hormones, hepatic impairment, diabetes mellitus, and increased blood glucose levels, as well as the safety in patients with hepatitis C infection. However, given the possibility that evolocumab may be used clinically over several decades, post-marketing information on the long-term safety of evolocumab (including the above listed events) should be collected because of the currently limited experience with long-term use. Appropriate measures should be taken when new findings become available. This conclusion of PMDA was supported by the expert advisors.

6. Risk management plan (draft)

The applicant submitted a plan for a specified drug use-results survey whereby data will be collected from 3000 patients during a 2-year observation period which should allow the detection of an adverse event with an incidence of 0.1% in at least 1 patient with 95% probability, including ≥300 patients with hepatic impairment and ≥300 elderly patients (≥75 years old). Taking account of the review described in the "4.(iii).B.(8) Post-marketing investigations" of the Review Report (1) and the comments raised by the expert advisors, PMDA has concluded that under the current risk management plan for evolocumab, the applicant should establish safety and efficacy specifications as listed in Table 46 and perform additional pharmacovigilance and risk minimization activities as shown in Table 47. The applicant submitted a risk management plan (draft) and a post-marketing surveillance plan (draft) based on Tables 46 and 47 (see Table 48 for the outline).

Table 46. Safety and efficacy specifications in risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
Not applicable	• Hypersensitivity • Immunogenicity	• HoFH patients (including pediatric patients) • Elderly patients (≥75 years) • Patients with hepatic impairment • Patients with HCV infection • Long-term use (including the effect of low LDL-C levels [<40 mg/dL])
Efficacy specification		
• Long-term efficacy in routine clinical use		

Table 47. Outline of additional pharmacovigilance and risk minimization activities in the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified drug use-results surveys (long-term use)	• Information provision based on the early post-marketing phase vigilance • Preparation and distribution of materials for healthcare professionals • Publication of the occurrence of adverse drug reactions of evolocumab on the webpage

Table 48. Outline of the plan for post-marketing surveillance (draft)

Objective	Study of the long-term safety and efficacy in routine clinical use
Survey method	Central registry system
Patient population	Patients with familial hypercholesterolemia or hypercholesterolemia at high cardiovascular risk who have had an inadequate response to HMG-CoA reductase inhibitors
Observation period	2 years after the start of treatment with evolocumab
Planned sample size	3000 patients (safety analysis set)
Main investigation items	Adverse events related to hypersensitivity and immunogenicity

7. Errors in counting adverse events

The applicant reported that there were errors in the counting of adverse events in the Japanese phase II study (Study 20110231). PMDA asked the applicant to explain the details of the counting errors, cause of the errors, and the effect of the errors on the safety evaluation of evolocumab.

The applicant's explanation:
Due to a failure of the system for detecting data inconsistency in Study 20110231, 3 adverse events (myalgia, constipation, and nasopharyngitis [1 event each]) which occurred in 2 subjects after dosing of the study drug were counted as those occurring before dosing. In addition, 4 similar events were found in 4 subjects in the foreign phase II studies (Studies 20101154[18)] and 20101155[19)]) (diastolic hypertension, abdominal pain, and sinusitis [1 subject each] in Study 20101154; paraesthesia [1 subject] in Study 20101155). All of the 7 adverse events noted in 6 subjects were non-serious. None of the events led to study drug discontinuation. The reanalysis of the corrected data did not necessitate a change in the conclusion concerning the safety. No errors in counting adverse events occurred in other clinical studies.

PMDA' view:
Taking account of the applicant's explanation, the corrected adverse event data had little effect on the safety evaluation of evolocumab, causing no change in the risk-benefit balance and no errors in counting adverse events occurred in other studies submitted for this application. For this reason, the observed errors do not affect the conclusion of the review. The applicant should establish a strict checking system to avoid similar errors in the future and should fully share information among parties concerned in operating the system.

18) A study in which evolocumab was administered alone to FH or HC patients with a 10-year Framingham Risk Score of ≤10%

19) A study in which evolocumab was administered in combination with statins to FH or HC patients

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

Document-based compliance inspection and data integrity assessment were conducted in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics for the data submitted in the new drug application. As a result, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

2. PMDA's conclusion on the results of on-site GCP inspection

On-site GCP inspection was conducted in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics for the data submitted in the new drug application (5.3.5A.1-11, 5.3.5A.1-12, 5.3.5A.1-13-1). As a result, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

IV. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the indications and dosage and administration as shown below, with the following condition for approval. Since the product is a drug with a new active ingredient, the re-examination period is 8 years. Neither the drug substance nor the drug product is classified as a poisonous drug or a powerful drug. The drug product is classified as a biological product.

[Indications]	Familial hypercholesterolemia, hypercholesterolemia The product should be used only in patients with high cardiovascular risk who have had an inadequate response to HMG-CoA reductase inhibitors.
[Dosage and administration]	Heterozygous familial hypercholesterolemia and hypercholesterolemia: The usual adult dosage of Evolocumab (Genetical Recombination) is 140 mg once every 2 weeks or 420 mg once every 4 weeks, administered as a subcutaneous injection. Homozygous familial hypercholesterolemia: The usual adult dosage of Evolocumab (Genetical Recombination) is 420 mg once every 4 weeks administered as a subcutaneous injection. Evolocumab 420 mg may be administered subcutaneously once every 2 weeks if an adequate response is not achieved. When used as an adjunct to LDL apheresis, Evolocumab may be started at a dose of 420 mg once every 2 weeks subcutaneously.
[Condition for approval]	The applicant is required to develop and appropriately implement a risk management plan.