Report on the Deliberation Results

June 01, 2016
Evaluation and Licensing Division
Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour, and Welfare

Brand Name	Praluent 75 mg Solution for Injection in Pre-filled Syringe Praluent 150 mg Solution for Injection in Pre-filled Syringe Praluent 75 mg Solution for Injection in Pre-filled Pen Praluent 150 mg Solution for Injection in Pre-filled Pen
Non-proprietary Name	Alirocumab (Genetical Recombination) (JAN*)
Applicant	Sanofi K.K.
Date of Application	August 06, 2015

Results of Deliberation

In its meeting held on May 27, 2016, 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 product nor its drug substance is classified as a poisonous drug or a powerful drug, and both are classified as biological products.

Conditions of approval

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Review Report

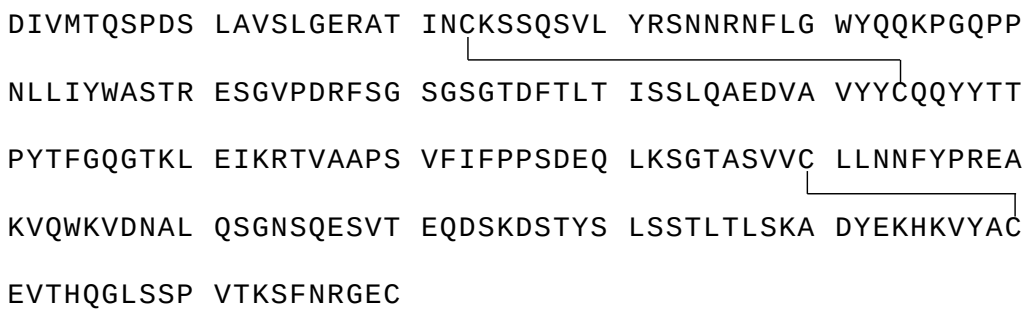
April 26, 2016
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand name	(a) Praluent 75 mg Solution for Injection in Pre-filled Syringe Praluent 150 mg Solution for Injection in Pre-filled Syringe (b) Praluent 75 mg Solution for Injection in Pre-filled Pen Praluent 150 mg Solution for Injection in Pre-filled Pen
Non-proprietary Name	Alirocumab (Genetical Recombination)
Applicant	Sanofi K.K.
Date of Application	August 06, 2015
Dosage Form/Strength	(a) Solution in a 1-mL syringe containing 75 mg or 150 mg of alirocumab (genetical recombination). (b) Solution in a 1-mL kit containing 75 mg or 150 mg of alirocumab (genetical recombination).
Application Classification	Prescription drug, (1) Drug with a new active ingredient
Definition	Alirocumab is a recombinant human IgG1 monoclonal antibody against human proprotein convertase subtilisin/kexin type 9 (PCSK9). Alirocumab is produced in Chinese hamster ovary cells. Alirocumab is a glycoprotein (molecular weight: ca. 149,000) composed of 2 H-chains (γ1-chains) consisting of 448 amino acid residues each and 2 L-chains (κ-chains) consisting of 220 amino acid residues each.

Chemical Structure

L-chain



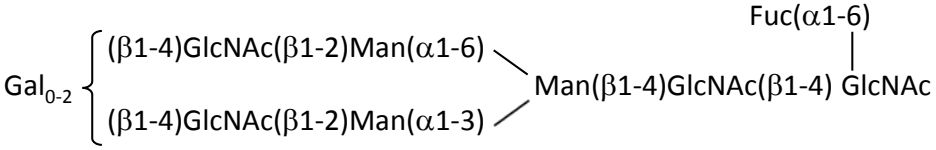
H-chain

Glycosylation: H-chain N298

Partial processing: H-chain K448

Disulfide bond: L-chain C220–H-chain C221, H-chain C227–H-chain C227, H-chain C230–H-chain C230

Putative structure of major sugar chains



Gal, galactose; GlcNAc, *N*-acetylglucosamine; Man, mannose; Fuc, fucose

Molecular formula: $C_{6484}H_{10020}N_{1740}O_{2034}S_{42}$ (proteins, four-stranded)

H-chain $C_{2170}H_{3362}N_{582}O_{669}S_{15}$

L-chain $C_{1072}H_{1652}N_{288}O_{348}S_6$

Molecular weight: Approximately 149,000

Items Warranting Special Mention None

Reviewing Office Office of New Drug II

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of familial hypercholesterolemia (FH) and hypercholesterolemia (HC) and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indications and dosage and administration as shown below, with the following conditions. However, further investigations are necessary for adverse events (AEs) of the product related to immunogenicity, systemic hypersensitivity reaction, cataract, and neurocognitive events; and the safety of the product in patients with homozygous familial hypercholesterolemia (HoFH) (including children), the elderly (aged ≥75 years), patients with hepatic impairment, and hepatitis C virus-positive patients.

Indications

Familial hypercholesterolemia and hypercholesterolemia

However, the use of the product should be limited to patients at high risk of cardiovascular events with an inadequate response to HMG-CoA reductase inhibitors

Dosage and Administration

The usual adult dosage is 75 mg of alirocumab (genetical recombination) administered by subcutaneous injection once every 2 weeks. The dose may be increased to 150 mg for patients not adequately responding to 75 mg.

Condition of Approval

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

March 15, 2016

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency.

Product Submitted for Approval

Brand Name	(a) Praluent 75 mg Solution for Injection in Pre-filled Syringe Praluent 150 mg Solution for Injection in Pre-filled Syringe (b) Praluent 75 mg Solution for Injection in Pre-filled Pen Praluent 150 mg Solution for Injection in Pre-Filled Pen
Non-proprietary Name	Alirocumab (Genetical Recombination)
Applicant	Sanofi K.K.
Date of Application	August 06, 2015
Dosage Form/Strength	(a) Solution in a 1-mL syringe containing 75 mg or 150 mg of alirocumab (genetical recombination). (b) Solution in a 1-mL kit containing 75 mg or 150 mg of alirocumab (genetical recombination).
Proposed Indications	Hypercholesterolemia and familial hypercholesterolemia However, the use of the product should be limited to: • Patients with inadequate response to HMG-CoA reductase inhibitors

Proposed Dosage and Administration

The usual adult dosage is 75 mg of alirocumab (genetical recombination) administered by subcutaneous injection once every 2 weeks. The dose may be increased to 150 mg once every 2 weeks for patients not adequately responding to the usual dosage.

Table of Contents

Product Submitted for Approval 1
1. Origin or History of Discovery, Use in Foreign Countries, and Other Information 7
2. Data Relating to Quality and Outline of the Review Conducted by PMDA 7
3. Non-clinical Pharmacology Data and Outline of the Review Conducted by PMDA 14
4. Non-clinical Pharmacokinetic Data and Outline of the Review Conducted by PMDA 26
5. Toxicity and Outline of the Review Conducted by PMDA 30
6. Summary of Biopharmaceutical Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA 41
7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA 56
8. Results of Compliance Assessment Concerning the New Drug Application and Conclusion Reached by PMDA 103
9. Overall Evaluation during Preparation of the Review Report (1) 103

List of Abbreviations

ACS	Acute coronary syndrome
ACTH	Adrenocorticotropic hormone
ADA	Anti-drug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
AEX	Anion exchange chromatography
Alirocumab	Alirocumab (genetical recombination)
ALT	Alanine aminotransferase
Apo A-1	Apolipoprotein A-1
ApoB	Apolipoprotein B
ApoE	Apolipoprotein E
$ApoE^{-/-}$	Apolipoprotein E-deficient
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC_{inf}	Area under the concentration-time curve computed from time zero to infinity
AUC_{last}	Area under the concentration-time curve computed from time zero to the time of the last positive concentration
AUC_{0-t}	Area under the concentration-time curve of the analyte in plasma
BA	Bioavailability
BMI	Body mass index
CAL	Cells at the limit of in vitro cell age used for production
CDC	Complement-dependent cytotoxicity
cDNA	Complementary DNA
CE-SDS	Capillary electrophoresis sodium dodecyl sulfate
CETP	Cholesteryl ester transfer protein
CHD	Coronary heart disease
CI	Confidence interval
CIEF	Capillary isoelectric focusing
CK	Creatine phosphokinase
CL	Total body clearance
CL/F	Apparent total body clearance
$C_{max, p}$	Maximum concentration of analyte in plasma
$C_{max, s}$	Maximum concentration of analyte in serum
$C_{max, ss}$	C_{max} at steady-state
CQA	Critical quality attribute
CV	Coefficient of variation
C1q	Complement component 1, q subcomponent
DNA	Deoxyribonucleic acid
ECL	Electrochemiluminescence
EC_{50}	Half maximal effective concentration
EGF	Epidermal growth factor
ELISA	Enzyme-linked immunosorbent assay
E_{max}	Maximum effect
EMCV	Encephalomyocarditis virus
EPC	End of production cells

ePPND	Enhanced pre- and postnatal development
FDA	Food and Drug Administration
FH	Familial hypercholesterolemia
GLP	Good laboratory practice
GLuc	Gaussia princeps-derived luciferase protein
GOF	Gain-of-function
HbA1c	Hemoglobin A1c
HC	Hypercholesterolemia
HCP	Host cell protein
HCV	Hepatitis C virus
HCVcc	HCV infectious virus produced in cell culture
HDF	Human dermal fibroblasts
HDL-C	High-density lipoprotein-cholesterol
HeFH	Heterozygous familial hypercholesterolemia
HLGT	High level group term
HLT	High level term
HoFH	Homozygous familial hypercholesterolemia
HPLC	High performance liquid chromatography
iCIEF	Imaged capillary isoelectric focusing
IC_{50}	Half maximal inhibitory concentration
IgG	Immunoglobulin G
IgM	Immunoglobulin M
ITT	Intent-To-Treat
IV	Intravenous
JAS Guidelines	Japan Atherosclerosis Society (JAS) Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2012
K_a	Primary absorption rate constant
K_D	Equilibrium dissociation constant
KLH	Keyhole limpet hemocyanin
K_m	Substrate concentration that produces half of the maximum reaction rate
K_{out}	First-order rate constant for loss of response
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein-cholesterol
LDLR	Low-density lipoprotein receptor
LLN	Lower limit normal
LOCF	Last Observation Carried Froward
Lp(a)	Lipoprotein (a)
mAb	Monoclonal antibody
MACE	Major adverse cardiac events (deaths due to coronary artery diseases, non-fatal myocardial infarction, fatal or non-fatal ischemic stroke, and angina unstable requiring hospitalization)
MCB	Master cell bank
MDRD	Modification of diet in renal disease
MFI	Median fluorescence intensity
mITT	Modified Intent-To-Treat

MMRM	Mixed-effect model with repeated measures
MMV	Mouse minute virus
mRNA	Messenger RNA
NK cell	Natural killer cell
non-FH	Non-familial hypercholesterolemia
non-HDL-C	Non-high-density lipoprotein-cholesterol
PBMC	Peripheral blood mononuclear cell
PBS	Phosphate-buffered saline
PCSA	Potentially clinically significant abnormality
PCSK9	Proprotein convertase subtilisin/kexin type 9
PD	Pharmacodynamic
PFP	Prefilled pen
PFS	Prefilled syringe
PMDA	Pharmaceuticals and Medical Devices Agency
PNGaseF	Peptide-*N*-glycosidase F
PPK	Population pharmacokinetic
Product	Praluent 75 mg or 150 mg Solution for Injection in Pre-Filled Syringe, and Praluent 75 mg or 150 mg Solution for Injection in Pre-Filled Pen
PRV	Pseudorabies virus
Q2W	Every 2 weeks
Q4W	Every 4 weeks
Regeneron	Regeneron Pharmaceuticals, Inc
Reo 3	Reovirus type 3
RNA	Ribonucleic acid
SC	Subcutaneous
SDS-PAGE	Sodium dodecyl sulfate-polyacrylamide gel electrophoresis
[redacted]	[redacted]
SE-HPLC	Size exclusion chromatography
SMQ	Standardised MedDRA (Medical dictionary for regulatory activities) queries
SPR	Surface plasmon resonance
Statin	HMG-CoA reductase inhibitor
TC	Total cholesterol
TG	Triglycerides
TK	Toxicokinetics
t_{max}	Time to reach the maximum serum concentration
$t_{1/2}$	Terminal half-life
ULN	Upper limit of normal
UV	Ultraviolet absorption spectroscopy
Vial formulation	Liquid formulation filled in glass vials
VLDL-C	Very low-density lipoprotein-cholesterol
V_{ss}	Volume of distribution at steady state
V2	Central compartment volume of distribution
V3	Peripheral volume of distribution
WCB	Working cell bank

X-MuLV	Xenotropic murine leukemia virus
2’CMA	2’C-methyl-adenosine
75 mg formulation	The formulation containing 75 mg of alirocumab (genetical recombination) (in syringe or pen)
150 mg formulation	The formulation containing 150 mg of alirocumab (genetical recombination) (in syringe or pen)

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Alirocumab, discovered by Regeneron Pharmaceuticals, Inc. (US), is a recombinant human IgG1 monoclonal antibody (mAb) against proprotein convertase subtilisin/kexin type 9 (PCSK9). Low-density lipoprotein receptors (LDLR) on the hepatocyte surface are essential for the uptake of plasma low-density lipoprotein-cholesterol (LDL-C) in hepatocytes. Proprotein convertase subtilisin/kexin type 9 (PCSK9) directly binds to LDLR, is taken into hepatocytes with low-density lipoprotein (LDL) and LDLR, and then causes decomposition of LDLR and increases in LDL-C levels in the circulation (*Trends Biochem Sci*. 2007;32:71-77). Alirocumab inhibits binding to LDLR by binding to PCSK9, and inhibits decomposition of LDLR in hepatocytes, thereby reducing LDL-C levels in the circulation.

Sanofi and Regeneron started the clinical development of alirocumab in 20[redacted]. As of January 2016, alirocumab has been approved in 33 countries including the US and Europe for the indication of "hypercholesterolemia (HC)."

In Japan, Sanofi-Aventis K.K. (currently Sanofi K.K.) started the clinical development of alirocumab in 20[redacted]. Recently, the application for market approval for the indications of "HC and familial hypercholesterolemia (FH)" was filed on the basis of clinical study data obtained in Japan and overseas.

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Preparation and control of cell substrates

Transgenic mice with immunoglobulin genes coding variable regions of heavy chains and κ-type light chains modified to the human sequence were immunized with human PCSK9, and B cells expressing anti-human PCSK9 antibody were isolated. Gene expression constructs of heavy and light chains were created using gene segments that coded the variable regions of heavy and light chains obtained from the isolated B cells, and plasmid that included the constant regions of heavy and light chains of human IgG1. These 2 gene expression constructs were introduced to a CHO cell line to obtain a new cell line (C1 cell line), and a cell bank was selected from the C1 cell line to use for development. Subsequently, a high expression line (C2 cell line) was newly generated, and a master cell bank (MCB) and a working cell bank (WCB) were prepared from the optimal clone for the manufacturing of alirocumab [see Section "2.1.4 Development of manufacturing process (equivalence/homogeneity)"].

Characterization (isozyme electrophoresis, DNA base sequencing analysis, cDNA base sequencing analysis, determination of gene copy number, southern or northern blot analysis) was performed on the MCB, WCB, end of production cells (EPC), and cells at the limit of in vitro cell age used for production (CAL). Genetic stability during manufacturing of the drug substance was confirmed.

MCB, WCB, EPC, and CAL were also tested for purity (sterility test, bacteriostatic test, mycoplasma test, bioburden test, adventitious virus test [*in vivo* and *in vitro*], hamster antibody production test, mouse antibody production test, swine virus test, bovine virus test, bovine polyoma virus test, S^+L^- focus assay,

reverse transcriptase activity or transmission electron microscopy). No adventitious virus or non-viral infectious substance was detected.

MCB and WCB are stored in [redacted] controlled at ≤[redacted]°C. While there is no plan for updating the MCB, the WCB are updated as needed.

2.1.2 Manufacturing process

The manufacturing process of the drug substance consists of the following steps: expanding culture; production culture; harvesting/filtration; [redacted]/virus inactivation at low pH; [redacted]; [redacted]; [redacted]; virus removal; [redacted]; formulation; and dispensing, testing, and storage. The obtained drug substance is dispensed to [redacted] and stored at [redacted]°C.

The manufacturing process was developed with a quality risk management approach. After specifying the critical quality attribute (CQA) below, process characterization and the identification of critical process parameters were performed to establish a quality control strategy.

- Specified CQA: Quality characteristics confirmed as [redacted], mycoplasma, adventitious virus and mouse minute virus (MMV), [redacted], [redacted] and endotoxin, [redacted]

[redacted], [redacted], [redacted], and [redacted] were defined as critical steps.

The process validation of the manufacturing process of the drug substance was performed at the actual production scale.

2.1.3 Safety evaluation of adventitious infectious substances

In the manufacturing process of the drug substance, CHO cell line (host cell) was the only biological material used. However, bovine milk-derived N-Z Amine is used for the manufacturing of puromycin contained in the medium for the preparation of the MCB and WCB, and swine-derived trypsin is used to manufacture N-Z Amine. These raw materials conformed to the Japanese Standards for Biological Ingredients.

Purity tests were performed on the MCB, WCB, EPC, and CAL [see Section "2.1.1 Preparation and control of cell substrates"]. Mycoplasma, bioburden, *in vitro* adventitious virus, and MMV were tested on the pre-harvest unpurified bulk obtained from production scale batches. None of these tests detected contamination by viral or non-viral adventitious infectious substances. The mycoplasma, bioburden, *in*

vitro adventitious virus, and MMV tests on the unpurified bulk were defined as the in-process control tests.

A virus clearance test was performed on the purification step using model viruses. The purification step was proven to achieve a certain level of viral clearance (Table 1).

Table 1. Results of virus clearance tests

Manufacturing step	Viral clearance factor (log_{10})				
	X-MuLV	MMV	PRV	EMCV	Reo 3
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Low pH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Virus filtration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total viral clearance factor	>16.9	>13.1	>17.2	>10.3	>13.1

[redacted]

2.1.4 Development of manufacturing process (equivalence/homogeneity)

The following major changes were made in the manufacturing method during the development of the drug substance (each manufacturing method was defined as the non-clinical method, Methods C1P1, C1P2, and C2P1 [manufacturing method for application], respectively). The phase I and II studies used drug products obtained from the drug substances manufactured by Method C1P1, C1P2, or C2P1. The phase III studies used the drug products obtained from the drug substance manufactured by Method C2P1.

- Non-clinical method → Method C1P1: Changes in [redacted], [redacted]
- Method C1P1 → Method C1P2: Changes in [redacted], [redacted], [redacted]
- Method C1P2 → Method C2P1: Changes in cell bank [redacted], [redacted], [redacted]

These changes required the evaluation of equivalence/homogeneity of the quality attributes. At the time of the change from Method C1P2 to C2P1, which involved the change of the cell bank to one derived from a cell line highly expressing C2, a non-clinical study [see Sections “3.1.2.6 Single intravenous and subcutaneous dose pharmacokinetic study in cynomolgus monkeys” and “4.1.1 Single-dose studies”] and a clinical study [see Section “6.1.2 Effect of difference in the manufacturing method of the drug substance on the PK of alirocumab”] were conducted. The results of these studies demonstrated the equivalence/homogeneity of the drug substance before and after the change in the manufacturing method.

2.1.5 Characterization

2.1.5.1 Structure

- The primary structure was analyzed by [redacted], [redacted], and tandem mass spectrometry.

- The higher-order structure was analyzed by [redacted].
- The carbohydrate structure and glycosylation site were analyzed by monosaccharide composition analysis, [redacted], PNGaseF processing liquid chromatography mass spectrometry (LC/MS), tandem mass spectrometry, and PNGaseF processing capillary electrophoresis.

2.1.5.2 Physicochemical characteristics

- The molecular weight was confirmed by electrospray ionization time-of-flight mass spectrometry (non-reduced, non-reduced deglycosylation, reduced deglycosylation).
- Size variants (in agglomerated and truncated forms) were confirmed by [redacted], non-reduced and reduced western blot, non-reduced and reduced SDS-PAGE/N terminal amino acid analysis, and non-reduced and reduced capillary electrophoresis sodium dodecyl sulfate (CE-SDS).
- Charge isoforms were confirmed by capillary isoelectric focusing (CIEF), reduced two-dimensional electrophoresis, and cation exchange chromatography.

2.1.5.3 Biological characteristics

- Surface plasmon resonance (SPR) confirmed that alirocumab has affinity to human and monkey PCSK9. Affinity to rat, mouse, and hamster PCSK9 was low. Affinity was increased in [redacted] as compared with that in [redacted] [see Section "3.1.1.1 Equilibrium binding constant for interactions with animal-derived PCSK9"].
- Using [redacted], the neutralization activity of alirocumab on the suppressive effect of PCSK9 on the LDL uptake was confirmed [see Section "3.1.1.3 Inhibition of suppression of LDL uptake by PCSK9 in cell-based bioassay"].
- No complement-dependent cytotoxicity (CDC) or antibody-dependent cell-mediated cytotoxicity (ADCC) activity of alirocumab was detected [see Section "3.2.2 Determination of Fc effector function activity in a cell-based bioassay"].
- The drug substance intermediates before formulation and human PCSK9 were mixed at different molar ratios; formation of a complex was confirmed at all molar ratios using [redacted]. The complex was formed at the ratio of alirocumab to human PCSK9 of [redacted] or [redacted].

2.1.5.4 Product-related substances and product-derived impurities

Based on the analysis results in the sections "2.1.5.1 Structure," "2.1.5.2 Physicochemical characteristics," and "2.1.5.3 Biological characteristics," the charge isoform and oxidant were identified to be product-related substances. The size variants (agglomerated and truncated forms) were identified to be product-related impurities. The charge isoform will be controlled by the specifications for the drug substance and drug product ([redacted]), oxidant by the specifications for the drug substance

([redacted]), agglomerated form by the specifications for the drug substance and drug product ([redacted]), and truncated form by the specifications for the drug substance and drug product ([redacted]).

2.1.5.5 Process-related impurities

Host cell protein (HCP), host cell-derived DNA, [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], bioburden, endotoxins, and [redacted] ([redacted]) were identified to be process-related impurities. All of these process-related impurities were removed thoroughly during the manufacturing process.

2.1.6 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (peptide mapping and imaged capillary isoelectric focusing [iCIEF]), osmolarity, pH, conductivity, purity (size exclusion chromatography [SE-HPLC], and non-reduced and reduced CE-SDS), charge inhomogeneity (iCIEF), endotoxins, bioburden, polysorbate 20, potency (cell bioassay), and assay (Ultraviolet absorption spectroscopy [UV]). During this review, sugar chain analysis [redacted] and purity (HCP and host cell-derived DNA) were included.

2.1.7 Stability of drug substance

The main stability tests for the drug substance are shown in Table 2.

Table 2. Main stability tests for drug substance

	Manufacturing method	Number of batches	Storage condition	Storage period (month)	Storage container
Long-term	C2P1	6[a]	−30 ± 10°C	24[b]	[redacted]
Accelerated		6[a]	25 ± 2°C	6	
Stress		6[a]	45 ± 3°C	6	
Photo-stability		1	Total illuminance of ≥1.2 Mlx·h, total near-ultraviolet radiation energy of ≥200 W·h/m^2, 25 ± 2°C		

[a] 3 batches each from 2 actual production areas.
[b] The stability testing is ongoing and will continue up to [redacted] months.

In the long-term testing, no apparent change was noted in the quality characteristics throughout the testing period.

In the accelerated testing, increased protein levels, [redacted], [redacted], [redacted], tendency toward increasing non-glycosylated forms and agglomerated forms, and [redacted] were noted.

In the stress test, [redacted] and [redacted] were noted in addition to the changes observed in the accelerated study.

The results of the photostability testing showed that the drug substance was unstable when exposed to light.

Accordingly, the shelf-life of the drug substance was determined to be [redacted] months when stored [redacted] under protection from light at [redacted] ± [redacted]°C.

2.2 Drug product

2.2.1 Description and composition of the drug product

The drug product is an injectable solution containing 75 or 150 mg of alirocumab pre-filled in a glass syringe (1 mL). There are two dosage forms: pre-filled syringe (Praluent 75 mg or 150 mg Solution for Injection in Pre-filled Syringe) and pen-type injector mounted with a pre-filled syringe (Praluent 75 mg or 150 mg Solution for Injection in Pre-filled Pen). The drug product contains L-histidine, L-histidine hydrochloride hydrate, sucrose, polysorbate 20, and water for injection as excipients.

Praluent in pre-filled syringe are [redacted]. Blister-packed syringes are packed in cartons. Praluent in pre-filled pen is a combination product consisting of a pen-type injector and a syringe assembled into the injector. Pillow-packed pens are packed in cartons.

2.2.2 Manufacturing process

The production of the 150 mg formulation involves the following steps: melting of the drug substance, mixing, pre-filtration, aseptic filtration, filling/plugging, syringe assembly, and labeling/packaging/storage/testing. [redacted], [redacted], [redacted], [redacted], and [redacted] were defined as critical steps.

The production of the 75 mg formulation follows the manufacturing process of the 150 mg formulation, except additional steps after mixing, namely, diluent preparation, diluent filtration, and dilution of the drug substance.

The manufacturing processes of the drug product were validated at the actual production scale.

2.2.3 Development of manufacturing process (equivalence/homogeneity)

During the development phase of the drug product, there were changes in the drug formulation, dosage form (from a lyophilized formulation to a solution, from vial to syringe and pen), production site, and production scale. When the manufacturing method of the drug product was modified, the

equivalence/homogeneity of the quality attributes were evaluated. The equivalence/homogeneity of the drug product before and after the modification was confirmed.

2.2.4 Control of drug product

The proposed specifications for the drug product consist of content, description, identification (iCIEF, enzyme-linked immunosorbent assay [ELISA]), pH, purity (SE-HPLC, reduced and non-reduced CE-SDS), charge inhomogeneity (iCIEF), bacterial endotoxins, extractable volume (for syringe formulation only), insoluble foreign matter, insoluble particulate matter, sterility, potency (cell bioassay), and assay (UV).

2.2.5 Stability of drug product

Table 3 shows the main stability tests for the drug product. The stability tests were performed on the drug product manufactured using the drug substance manufactured by Method C2P1.

Table 3. Main stability tests for the drug product

	Number of batches[a]	Storage condition	Storage period (month)	Storage container[b]
Long-term	4	5 ± 3°C	24[c]	Glass syringe
Accelerated	4	25 ± 2°C	6	
Stress	2	45 ± 3°C	6	
Photostability	1	Total illuminance of ≥1.2 Mlx·h, total near-ultraviolet radiation energy of ≥200 W·h/m^2, 25 ± 2°C		

[a] The number of batches for each of the 75 mg and 150 mg formulations
[b] Because a pre-filled syringe is assembled into the pen-type product as its primary container, the long-term testing, accelerated testing, stress test, and photostability testing were performed on some pieces of the pen-type products as well.
[c] The stability testing is ongoing and will continue up to [redacted] months.

In the long-term testing, no clear change was noted in the quality characteristics.
In the accelerated testing, [redacted] and [redacted], [redacted], [redacted], [redacted] and [redacted] were noted.

In the stress test, in addition to the changes as in the accelerated testing, color change and reduced potency were noted.

The photostability testing revealed instability of the drug product when exposed to light.

Accordingly, the shelf-life of the 75 mg and 150 mg formulations was determined as 24 months when stored under protection from light at 2°C to 8°C.

2.3 Reference materials

The primary reference material and working reference material are prepared from the drug substance or drug substance before formulation, and stored at [redacted] ± [redacted]°C. The proposed specifications for the reference materials include content, description, identification (peptide mapping, ELISA), osmolality, pH, conductivity, purity ([redacted], [redacted]), charge inhomogeneity ([redacted]), mean molecular weight ([redacted]), sugar chain analysis ([redacted]), peptide mapping analysis (non-reduced, reduced alkylation), secondary structure ([redacted]), structural analysis ([redacted]), potency ([redacted]), and assay (UV).

2.R Outline of the review conducted by PMDA

Based on the data submitted and the following reviews, PMDA concluded that the quality of the drug substance, drug product, syringe, and injection pen is adequately controlled.

2.R.1 Control of biological activity

To control the biological activity of alirocumab, the proposed specifications for the drug substance and drug product include a potency test using [redacted] cells to determine the inhibition activity of drug product against PCSK9's suppressive effect on LDL uptake. During development, dose-response curves for potency calculation and study validity requirements were modified to improve the accuracy of the test method. The test results of [redacted] batches of the drug substance and drug product, which were submitted as the rationale for the specification limits, were obtained from both the initial and modified methods. Because of significant variations in the test results of the [redacted] batches based on the initial test method as compared to those based on the modified test method, PMDA requested the applicant to redefine the specification limits only based on the test results obtained by the modified method for controlling the specifications within appropriate ranges.

The applicant's explanation:

At the time of the application, only limited data were available from the modified test method. The specification limits will be reviewed and redefined based on the test results of [redacted] batches obtained by the test modified method and including additional batch-specific data and stability data of the drug substance and drug product obtained later.

PMDA accepted the applicant's response.

3. Non-clinical Pharmacology Data and Outline of the Review Conducted by PMDA

3.1 Primary pharmacodynamics

3.1.1 *In vitro* studies

3.1.1.1 Equilibrium binding constant for interactions with animal-derived PCSK9 (CTD 4.2.1.1-1)

A PCSK9 solution was sent over the surface of a sensor chip capturing alirocumab with anti-human Fc at 25°C and pH 7.4, and a binding test was performed using the SPR method. The K_D values for binding

of alirocumab to wild-type human PCSK9, GOF mutant (D374Y) human PCSK9, and cynomolgus monkey, rat, mouse, and hamster-derived PCSK9 were approximately 0.58, 1.69, 0.52, 14.50, 2.61, and 6.81 nmol/L, respectively.

A PCSK9 solution was sent over the surface of a sensor chip capturing alirocumab by amine coupling at 25°C and pH 7.4 (neutral) or pH 5.5 (acid), and a binding test was performed using the SPR method. The K_D values for binding of alirocumab to wild-type human PCSK9, GOF mutant (D374Y) human PCSK9, and cynomolgus monkey, rat, mouse, and hamster-derived PCSK9 were 1.26, 2.49, 1.42, 24.1, 4.46, and 8.35 nmol/L, respectively, at pH 7.4, and 0.022, 0.166, 0.058, 0.349, 0.063, and 0.087 nmol/L, respectively, at pH 5.5.

3.1.1.2 Inhibition of binding of PCSK9 to human LDLR extracellular domain in blocking ELISA (CTD 4.2.1.1-2)

The inhibitory effect of alirocumab on the binding of animal-derived PCSK9 to 3 types of human LDLR (complete LDLR extracellular domain, receptor-type containing EGF-A and EGF-B domains, and receptor-type containing EGF-A domain only) was evaluated by blocking ELISA.

Alirocumab inhibited the binding of wild-type human PCSK9 (0.5 nmol/L) to each human LDLR, and IC_{50} values of alirocumab were below the limit of quantification (BLQ) (0.125 nmol/L) for all LDLR at pH 7.2, and BLQ to 0.17 nmol/L at pH 5.5. Alirocumab inhibited the binding of GOF mutant (D374Y) human PCSK9 (0.05 nmol/L) to each human LDLR, with IC_{50} values of 0.17 to 0.23 nmol/L at pH 7.2 and 1.1 to 1.7 nmol/L at pH 5.5. Alirocumab also inhibited binding of cynomolgus monkey, rat, mouse, and hamster derived PCSK9 to each human LDLR at pH 7.2 and pH 5.5. IC_{50} values were BLQ (0.250 nmol/L in the studies using rat, mouse, and hamster-derived PCSK9, and 0.075 nmol/L in the study using cynomolgus monkey derived PCSK9) to 15.6 nmol/L.

3.1.1.3 Inhibition of the suppression of LDL uptake by PCSK9 in cell-based bioassay (CTD 4.2.1.1-2)

A cell-based assay was performed using HepG2 cells highly expressing LDLR to evaluate the inhibitory effect of alirocumab on the suppression of LDL uptake by animal-derived PCSK9.

Wild-type human PCSK9 and GOF mutant (D374Y) human PCSK9 inhibited the uptake of BODIPY-labeled LDL into HepG2 cells in a concentration-dependent manner, and the EC_{50} values were 18 and 0.7 nmol/L, respectively. Cynomolgus monkey, rat, mouse, and hamster-derived PCSK9 inhibited the uptake of BODIPY-labeled LDL into HepG2 cells in a concentration-dependent manner, and the EC_{50} values were 20 to 34 nmol/L.

When alirocumab was added at various concentrations in the presence of a specific amount of PCSK9, alirocumab inhibited the suppressive effect of wild-type human PCSK9 (50 nmol/L) and GOF mutant (D374Y) human PCSK9 (1 nmol/L) on the uptake of BODIPY-labeled LDL into HepG2 cells in a

concentration-dependent manner, and the IC_{50} values were 22 and 2.1 nmol/L, respectively. Alirocumab inhibited the suppressive effect of cynomolgus monkey, rat, mouse, and hamster-derived PCSK9 (50 nmol/L) on the uptake of BODIPY-labeled LDL into HepG2 cells in a concentration-dependent manner, and the IC_{50} values were 19 to 27 nmol/L.

3.1.1.4 Suppression of PCSK9-mediated down-regulation of LDLR in HDF deriving from HoFH patients with LDLR activity-deficient mutation (CTD 4.2.1.1-3)

The suppressive effect of alirocumab on PCSK9-mediated down-regulation of cell surface LDLR was evaluated using human dermal fibroblasts (HDF) deriving from *LDLR*-deficient (>2% of normal LDLR activity) and *LDLR*-null (<2% of normal LDLR activity) HoFH patients, HDF deriving from healthy subjects, and HDF deriving from HeFH patients. In a 0.5% serum-containing medium, mevastatin 40 μg/mL was added to allow the HDF to proliferate. After incubating each HDF with wild-type human PCSK9 (0-6000 ng/mL) or GOF mutant (D374Y) human PCSK9 (0-600 ng/mL) for 4 hours in the presence and absence of alirocumab (600-19,200 ng/mL), LDLR expression levels on the cell surface were determined by flow cytometry.

LDLR expression levels (median fluorescence intensity [MFI]) (mean ± standard error [SE]) at baseline (in the absence of alirocumab and PCSK9) were 5636 ± 605 in HDF deriving from healthy subject-derived, 2297 ± 198 in that from HeFE patients, 799 ± 89 in that from *LDLR*-deficient HoFH patients, and 216 ± 20 in that from *LDLR*-null HoFH patients. After the addition of wild-type human PCSK9 at the maximum concentration (6000 ng/mL), LDLR expression was suppressed by 85% in HDF deriving from healthy subjects, 66% in that from HeFH patients, and 57%in that from *LDLR*-deficient HoFH patients. After the addition of GOF mutation (D374Y) human PCSK9 at the maximum concentration (600 ng/mL), LDLR expression was suppressed by 89% in HDF deriving from healthy subjects, 71% in that from HeFH patients, and 71% in that from *LDLR*- deficient HoFH patients. In HDFs deriving from healthy subjects, HeFH patients, and *LDLR*- deficient HoFH patients, alirocumab inhibited the suppressive effect of wild-type human PCSK9 and GOF mutant (D374Y) human PCSK9 on LDLR expression in a concentration-dependent manner. After the addition of alirocumab at the maximum concentration (19,200 ng/mL), LDLR expression increased significantly in all HDFs as compared with that without alirocumab. On the other hand, in HDF deriving from *LDLR*-null HoFH patients, little effect on LDLR expression was noted after the addition of wild-type human PCSK9 and GOF mutant (D374Y) human PCSK9. There was no significant change in the suppressive effect on cell surface LDLR expression after the addition of wild-type human PCSK9, GOF mutant (D374Y) human PCSK9, and alirocumab as compared with the effect without alirocumab.

3.1.2 *In vivo* studies

3.1.2.1 C57BL/6 mice (CTD 4.2.1.1-5, 4.2.1.1-7)

A single intravenous human PCSK9 (30 μg/mouse, approximately 1.2 mg/kg) or vehicle (phosphate-buffered saline [PBS]) was given to mature male C57BL/6 mice. In the PCSK9 group, hepatic LDLR protein levels significantly decreased at 4 hours postdose and serum LDL-C concentrations significantly

increased at 8 hours postdose as compared with those in the vehicle group (4-5 mice/group at each sampling point).

A single intraperitoneal alirocumab 5, 10, and 30 mg/kg or isotype control antibody was given to mature male C57BL/6 mice. The mice then received human PCSK9 (30 μg/mouse) or vehicle (PBS) 18 hours later. After a 6-hour interval, serum LDL-C concentrations were determined (4 mice). The increases in serum LDL-C concentrations after the administration of PCSK9 were suppressed in a dose-dependent manner in the alirocumab groups as compared with those in the isotype control antibody group. After the administration of PBS, serum LDL-C concentrations tended to decrease in the alirocumab groups as compared with those in the isotype control antibody group.

3.1.2.2 *Pcsk9*$^{hum/hum}$ mice (CTD 4.2.1.1-6, 4.2.1.1-7)

A single intraperitoneal alirocumab 5 mg/kg or isotype control antibody was given to male *Pcsk9*$^{hum/hum}$ mice (8-12 weeks of age) that had their both alleles of mouse *Pcsk9* gene replaced with human *PCSK9* gene. The mice then received human PCSK9 intravenously 20 hours later. After a 4-hour interval, LDLR protein levels in the liver, brain, lungs, kidney, heart, ileum, adrenal gland, and pancreas were determined and a microarray analysis was performed (3 mice/group). While alirocumab increased hepatic LDLR levels at 24 hours postdose as compared with those in the isotype control group, it did not affect LDLR levels in the organs other than the liver. The microarray analysis showed that alirocumab inhibited increases in expression of genes involved in human PCSK9-mediated lipid metabolism and biosynthesis/metabolism of sterol.

A single intraperitoneal alirocumab 5 mg/kg or isotype control antibody was administered to *Pcsk9*$^{hum/hum}$ mice (8-12 weeks of age). Human PCSK9 was then intravenously administered 18 hours later, and serum LDL-C concentrations were determined after a 6 hour interval (4 mice/group). Alirocumab inhibited increases in LDL-C concentrations by PCSK9 as compared with isotype control antibody.

A single subcutaneous alirocumab 1, 5, and 10 mg/kg, or vehicle (PBS) was administered to *Pcsk9*$^{hum/hum}$ mice (8-12 weeks of age) with serum human PCSK9 and LDL-C concentrations increased after 6-week consumption of high-carbohydrate meals (carbohydrates 66.4%). Serum LDL-C concentrations at 24 hours postdose decreased in the alirocumab groups as compared with those in the vehicle group. The decreases were dose-dependent, and the serum LDL-C concentrations recovered to baseline in the 10 mg/kg group (4 mice/group).

3.1.2.3 *Pcsk9*$^{hum/hum}$ *Ldlr*$^{+/-}$ mice (CTD 4.2.1.1-8)

A single subcutaneous alirocumab 10 mg/kg or control antibody (anti-human-interleukin-4 receptor IgG4^{P} antibody) was administered to mature male humanized PCSK9 mice with an allelic loss of mouse *Ldlr* gene (*Pcsk9*$^{hum/hum}$ *Ldlr*$^{+/-}$ mice) (11-12 weeks of age). Serum LDL-C concentrations were determined over time up to 14 days postdose (5 mice/group). The reduction rate of serum LDL-C in the alirocumab group compared with that in the control antibody group was highest at approximately 35%

on Day 4 of administration. The serum LDL-C concentrations recovered to the baseline values on Day 11. In the alirocumab group, serum alirocumab was detected until Day 11.

3.1.2.4 *ApoE*$^{-/-}$ mice (CTD 4.2.1.1-7)

A single subcutaneous alirocumab 5 mg/kg or isotype control antibody was administered to male *ApoE*$^{-/-}$ mice (8 weeks of age) with defective *ApoE* gene. Serum LDL-C concentrations at 24 hours postdose (5 mice/group) decreased from baseline by 27% in the alirocumab group and were similar to the baseline values in the control antibody group.

3.1.2.5 Golden Syrian hamsters (CTD 4.2.1.1-10)

A single subcutaneous alirocumab 1, 3, or 10 mg/kg or vehicle (PBS) was administered to male golden Syrian hamsters (6-8 weeks of age), and serum lipid concentrations were determined at 1, 7, 14, 21, and 28 days postdose (6 hamsters/group). In the alirocumab groups, serum LDL-C and total cholesterol (TC) concentrations decreased in a dose-dependent manner as compared with those in the vehicle group. While serum HDL-C concentrations slightly decreased as compared with those in the vehicle group, no change was noted in serum triglyceride (TG) concentrations. In the alirocumab 10 mg/kg group, serum LDL-C and TC concentrations were lowest at 7 days postdose, with the mean reduction rates of 60% and 28%, respectively. Both concentrations recovered to baseline by 28 days postdose. In the alirocumab 10 mg/kg group, serum alirocumab was detectable until 21 days postdose and was not detected at 28 days postdose.

3.1.2.6 Single intravenous and subcutaneous dose pharmacokinetic study in cynomolgus monkeys (CTD 4.2.2.7-1)

A single intravenous or subcutaneous alirocumab 5 mg/kg produced using the C1 cell line (cell line used in the non-clinical, phase I, and phase II studies) or C2 cell line (cell line used in the phase III study) was administered to male cynomolgus monkeys (3-5 years of age), and blood was collected over time until 52 days postdose (6 monkeys/group). In all treatment groups, serum TC concentrations decreased after administration of alirocumab. Serum LDL-C concentrations decreased from baseline significantly from 48 hours postdose in all treatment groups and continued to decrease until 16 days postdose. Serum LDL-C concentrations then began to increase at 16 to 22 days postdose and recovered baseline by 26 days postdose. Serum HDL-C concentrations tended to decrease from baseline slightly at 48 hours postdose and continued to decrease until 13 days postdose in all treatment groups. In these changes, there was no difference in the effect on serum lipid between C1 cell strain-derived alirocumab and C2 cell strain-derived alirocumab.

3.1.2.7 Single intravenous dose pharmacokinetic study in cynomolgus monkeys (CTD 4.2.1.1-11)

A single intravenous alirocumab 5 or 15 mg/kg or vehicle (sodium phosphate buffer) was administered to male cynomolgus monkeys (4.3-5.8 years of age), and blood was collected over time until 102 days postdose (3 monkeys/group). Serum LDL-C concentrations began to decrease at 12 hours postdose in a dose-dependent manner in the alirocumab groups as compared with those in the vehicle group. In most

monkeys, serum LDL-C concentrations decreased to lowest values by 7 days postdose and recovered to baseline by 57 days postdose. Serum TC concentrations also decreased dose-dependently in the alirocumab groups as compared with those in the vehicle group. Serum TC concentrations decreased to lowest values at 7 days postdose and recovered to baseline at 57 days postdose.

3.1.2.8 Single intravenous and subcutaneous dose pharmacokinetic study in cynomolgus monkeys (CTD 4.2.2.2-3)

A single intravenous alirocumab 1, 3, or 15 mg/kg or single subcutaneous alirocumab 1 or 15 mg/kg was administered to male and female cynomolgus monkeys (2.5-5.5 years of age), and blood was collected over time until 52 days postdose (3 male and 3 female monkeys/group). Serum LDL-C and TC concentrations decreased from 48 hours postdose generally in a dose-dependent manner. The degree of decreases in LDL-C and TC concentrations were similar between the intravenous and subcutaneous doses, except for serum LDL-C concentrations after the subcutaneous doses showing a slightly larger decrease than those after intravenous dose in females in the 15 mg/kg group. LDL-C and TC concentrations continued to decrease after the dose of alirocumab 1, 3, and 15 mg/kg for 10, 16, and 30 days, respectively. There was no change associated with alirocumab in serum HDL-C concentrations. Serum TG concentrations tended to show minor and dose-independent decreases at 48 and 96 hours postdose in all monkeys except males in the subcutaneous 1 mg/kg group. In female monkeys, the duration of decreases in TG concentrations differed depending on the route of administration; it continued up to 10 days in the intravenous 3 and 15 mg/kg groups and up to 16 days in the subcutaneous 15 mg/kg group.

3.2 Secondary pharmacology

3.2.1 Binding affinity to subtilisin proteases other than PCSK9

The binding affinity of alirocumab was evaluated using proteins other than PCSK9 (PCSK1 and PCSK7) in the subtilisin protease family. Alirocumab did not bind to either non-PCSK9 subtilisin protease (US patent 20100166768; July 1, 2010).

3.2.2 Determination of Fc effector function activity in a cell-based bioassay (CTD 4.2.1.2-1)

A cell-based bioassay was performed to evaluate the effect of alirocumab on ADCC and CDC using SW13 cells, HUVEC cells, HepG2 cells, and HEK293 cells overexpressing human LDLR. When alirocumab (1.7 pmol/L-100 nmol/L) was added to these cell strains with human normal serum containing peripheral blood mononuclear cells (PBMC) or complement components either in the presence or absence of human PCSK9 (10 nmol/L), no ADCC or CDC was detected in any of these cells strains.

3.2.3 Determination of complement activation immune complex formation (CTD 4.2.1.2-1)

The possibility that alirocumab-PCSK9 complex forms complement activation immune complexes with C1q binding capacity was investigated. Alirocumab 10 and 50 nmol/L were incubated with human PCSK9 at an equimolar ratio, and were added to C1q protein coated on a plate. Concentrations of

immune complex bound to C1q were determined by ELISA using anti-human IgG. Alirocumab did not form any immune complex in the presence of PCSK9 at either concentration.

3.3 Safety pharmacology

3.3.1 Effects on the central nervous, cardiovascular, and respiratory systems (CTD 4.2.3.2-1 to 4.2.3.2-5, 4.2.3.2-7 to 4.2.3.2-12, 4.2.3.5.3-1)

The effects of alirocumab on the central nervous, cardiovascular, and respiratory systems are summarized in Table 4.

Table 4. Summary of safety pharmacological data

Item	Test system	Evaluation item and method	Dose of alirocumab	Route of admini-stration	Finding	CTD
Central nervous system (CNS)	SD rats (15 males and females each/group)	Observation of general condition	0, 0.5, 5, 15, 75 mg/kg once weekly, 16 days	IV	No effect on CNS	4.2.3.2-1
	SD rats (15 males and females each/group)	Observation of general condition	0, 0.5, 5, 15, 75 mg/kg once weekly, 5 weeks	SC	No effect on CNS	4.2.3.2-2
	SD rats (15 males and females each/group)	Observation of general condition	0, 5, 15, 75 mg/kg once weekly, 13 weeks	IV	No effect on CNS	4.2.3.2-3
			50 mg/kg, once weekly, 13 weeks	SC		
	SD rats (15 males and females each/group)	Observation of general condition	0, 5, 15, 50 mg/kg once weekly, 26 weeks	SC	No effect on CNS	4.2.3.2-4
			30 mg/kg, once weekly, 26 weeks	IV		
	Cynomolgus monkeys (5 males and females each/group)	Observation of general condition	0, 0.5, 5,15, 75 mg/kg once weekly, 16 days	IV	No effect on CNS	4.2.3.2-5
	Cynomolgus monkeys (5 males and females each/group)	Observation of general condition	0, 0.5, 5, 15, 75 mg/kg once weekly, 5 weeks	SC	No effect on CNS	4.2.3.2-7
	Cynomolgus monkeys (6 males and females each/group)	Observation of general condition	0, 5, 15, 75 mg/kg once weekly, 13 weeks	IV	No effect on CNS	4.2.3.2-8
	Cynomolgus monkeys (6 males and females each/group)	Observation of general condition	0, 5, 15, 75 mg/kg once weekly, 26 weeks	SC	No effect on CNS	4.2.3.2-9
			50 mg/kg, once weekly, 26 weeks	IV		
	Cynomolgus monkeys (5 males and females each/group)	Observation of general condition	0, 15 mg/kg, once weekly, 5 weeks alone or in combination with atorvastatin (0, 10, 50 mg/kg, once daily, intranasal)	IV	No effect on CNS	4.2.3.2-10
	Cynomolgus monkeys (6 males and females each/group)	Observation of general condition	0, 75 mg/kg, once weekly, 13 weeks alone or in combination with atorvastatin (0, 25, 40 mg/kg, once daily, intranasal)	IV	No effect on CNS	4.2.3.2-12
	Pregnant cynomolgus monkeys (20 females/group)	Observation of general condition	0, 15, 75 mg/kg once weekly from Day 20 of gestation until delivery	SC	No effect on CNS	4.2.3.5.3-1
Cardiovascular system	Cynomolgus monkeys (5 males and females each/group)	Blood pressure, electrocardio-graphy (under anesthesia)	0, 0.5, 5, 15, 75 mg/kg once weekly, 16 days	IV	No significant effect	4.2.3.2-5
	Cynomolgus monkeys (5 males and females each/group)	Blood pressure, electrocardio-graphy (under anesthesia)	0, 0.5, 5, 15, 75 mg/kg once weekly, 5 weeks	SC	No significant effect	4.2.3.2-7

Item	Test system	Evaluation item and method	Dose of alirocumab	Route of admini-stration	Finding	CTD
	Cynomolgus monkeys (6 males and females each/group)	Blood pressure, electrocardio-graphy (under anesthesia)	0, 5, 15, 75 mg/kg once weekly, 13 weeks	IV	No significant effect	4.2.3.2-8
	Cynomolgus monkeys (6 males and females each/group)	Blood pressure, electrocardio-graphy (under anesthesia)	0, 5, 15, 75 mg/kg once weekly, 26 weeks	SC	No significant effect	4.2.3.2-9
			50 mg/kg, once weekly, 26 weeks	IV		
	Cynomolgus monkeys (5 males and females each/group)	Blood pressure, electrocardio-graphy (under anesthesia)	0, 15 mg/kg, once weekly, 5 weeks alone or in combination with atorvastatin(0, 10, 50 mg/kg, once daily, intranasal)	IV	No significant effect	4.2.3.2-10
	Cynomolgus monkeys (6 males and females each/group)	Blood pressure, electrocardio-graphy (under anesthesia)	0, 15 mg/kg, once weekly, 13 weeks alone or in combination with atorvastatin (0, 10, 25 mg/kg, once daily, intranasal)	IV	No significant effect	4.2.3.2-11
Respi-ratory system	SD rats (15 males and females each/group)	Observation of general condition	0, 5, 15, 50 mg/kg once weekly, 26 weeks	SC	No effect on respiratory system	4.2.3.2-4
			30 mg/kg, once weekly, 26 weeks	IV		

3.3.2 CD81 expression and HCV invasion of hepatocytes (CTD 4.2.1.3-1, non-GLP)

After incubation of Huh-7 cells with alirocumab (200 or 300 μmol/L) or its isotype control antibody, and with wild-type human PCSK9 (5-500 nmol/L) or GOF mutant (D374Y) human PCSK9 (0.2-20 nmol/L), cell surface and intracellular expression levels of LDLR and CD81 were determined by flow cytometry and western blotting. Although both measurements revealed decreased LDLR expression in a manner dependent on the PCSK9 dose, no correlation was noted between PCSK9 concentrations and CD81 expression levels. Both measurements also revealed increased LDLR expression after the addition of alirocumab as compared with those after the addition of isotype control antibody. No change was noted in CD81 expression levels.

Serum LDL-C concentrations and hepatic LDLR and CD81 expression levels were determined using serum and liver tissues sampled from male *Pcsk9*$^{-/-}$ mice and litter male wild-type mice (both 9 weeks of age) (4-5 mice each). In *Pcsk9*$^{-/-}$ mice, hepatic LDLR expression increased while serum LDL-C concentrations decreased as compared with wild-type control mice, but no change was noted in CD81 expression levels. After the subcutaneous dose of alirocumab 10 mg/kg or isotype control antibody to *Pcsk9*$^{hum/hum}$ *Ldlr*$^{+/-}$ mice (5 mice per group), hepatic LDLR expression increased while serum LDL-C concentrations decreased at 4 days postdose in the alirocumab group as compared with the control group. No change was noted in hepatic CD81 expression levels.

After incubation of Huh-7 cells with alirocumab 300 nmol/L or its isotype control antibody, and with wild-type human PCSK9 (5-500 nmol/L) or GOF mutant (D374Y) human PCSK9 (0.2-20 nmol/L), the cells were infected with hepatitis C virus (HCV) pseudo particles expressing firefly luciferase, and intracellular luciferase levels were determined at 48 hours after infection. Intracellular luciferase expression levels after the addition of alirocumab were the similar to those after the addition of the

isotype control antibody in either PCSK9. Alirocumab did not affect the invasion efficiency of HCV pseudo particles into cells.

After transfection of HCV subgenomic replicon expressing GLuc prepared from the JFH-1 strain to Huh-7 cells, the cells were incubated with alirocumab 300 nmol/L or its isotype control antibody, wild-type human PCSK9 (5-500 nmol/L), or GOF mutant (D374Y) human PCSK9 (0.2-20 nmol/L).GLuc secretion levels were determined at 6, 24, and 48 hours after transfection. GLuc secretion increased over time after the addition of alirocumab or the isotype control antibody with either PCSK9, showing similar values to those with no addition. Alirocumab thus did not affect HCV replication.

Huh-7 cells were incubated with alirocumab 300 nmol/L or its isotype control antibody, and with wild-type human PCSK9 (5-500 nmol/L) or GOF mutant (D374Y) human PCSK9 (0.2-20 nmol/L). Subsequently, these cells were infected with HCV infectious virus produced in cell culture (HCVcc), and GLuc secretion levels were determined 48 hours after incubation to evaluate the effect of alirocumab on the HCV lifecycle (invasion, genome replication, morphogenesis, release). The GLuc secretion levels after the addition of alirocumab or the isotype control antibody were similar to those with no addition of either PCSK9. Alirocumab thus did not affect the course of HCVcc infection.

3.4 Pharmacodynamic drug interactions

3.4.1 *APOE*3Leiden.*CETP mice (CTD 4.2.1.4-1)

Female *APOE*3Leiden.*CETP mice (9-13 weeks of age) expressing human variant *APOE* gene and human cholesteryl ester transfer protein (CETP) were fed a high fat, high cholesterol diet (with 15% cocoa butter and 0.15% cholesterol) from 3 weeks before administration of the study drug. The animals were then treated with alirocumab alone or the combination of alirocumab 3 or 10 mg/kg/week (subcutaneous) and atorvastatin 3.6 mg/kg/day (oral) for 18 weeks. Animals in the control group received an isotonic sodium chloride solution subcutaneously (15-20 mice/group).

Plasma lipid levels were determined during the study. Plasma TC concentrations in the alirocumab or atorvastatin alone group were lower than those in the control group. Plasma TC concentrations in the alirocumab + atorvastatin groups were lower than those in the alirocumab or atorvastatin alone group. The decreases in Plasma TC concentrations were seen in a manner dependent on the alirocumab dose. Plasma TG concentrations were lower in the alirocumab alone groups and higher in the atorvastatin alone group as compared with the control group. Plasma TG concentrations in the alirocumab + atorvastatin groups were lower than those in the atorvastatin alone group and were similar to those in the control group. Plasma HDL-C concentrations in the treatment groups (alirocumab alone, atorvastatin alone, or alirocumab + atorvastatin) did not differ from those in the control group.

At 18 weeks postdose, the liver was sampled to determine hepatic LDLR and free cholesterol levels. In the alirocumab alone and alirocumab/atorvastatin groups, hepatic LDLR increased in a manner dependent on the alirocumab dose as compared with the control group. In the atorvastatin alone group,

on the other hand, no significant change was noted in hepatic LDLR levels as compared with the control group. Hepatic free cholesterol levels in the treatment groups (alirocumab alone, atorvastatin alone, or alirocumab/atorvastatin) did not show a different trend from those in the control group.

Atherosclerotic lesions in the aortic root region was evaluated at 18 weeks postdose. The areas of atherosclerotic lesions were smaller in the alirocumab or atorvastatin alone group than in the control group. In the alirocumab + atorvastatin groups, the areas of atherosclerotic lesions decreased in a manner dependent on the alirocumab dose, and were smaller than those in the alirocumab or atorvastatin alone group. In the alirocumab or atorvastatin alone group, there were more lesion-free sections and fewer severe lesions than in the control group. In the alirocumab + atorvastatin groups, there were more lesion-free sections and fewer severe lesions than in the alirocumab or atorvastatin alone group. While the total plaque area on the aortic arch was smaller in the alirocumab alone groups than in the control group, no significant change was noted in that in the atorvastatin alone groups as compared with the control group. In the alirocumab + atorvastatin groups, the total plaque area on the aortic arch was smaller than in the alirocumab or atorvastatin alone group.

Furthermore, the plaque composition in severe atherosclerotic lesions was analyzed. The lesion stability index, which is used as a plaque instability parameter, was calculated by dividing the sum of the smooth muscle cell (SMC) area and collagen area in capsula fibrosa (plaque stabilizing factor) by the sum of the macrophage component and necrotic component including cholesterol cleft (plaque destabilizing factor). The alirocumab monotherapy groups were revealed to have higher plaque stabilizing factor, lower plaque destabilizing factor, and higher lesion stability index than those in the control group. In the atorvastatin alone group, the plaque stabilizing factor, plaque destabilizing factor, and the lesion stability index were similar to those of the control group. In the alirocumab + atorvastatin groups, the lesion stability index increased in a manner dependent on the alirocumab dose, and was higher than those of the alirocumab or atorvastatin alone group.

3.R Outline of the review conducted by PMDA

3.R.1 Serum LDL-C lowering effect of alirocumab

The applicant's explanation:

In *in vitro* studies, alirocumab bound to PCSK9 with high affinity and inhibited the suppressive effect of PCSK9 on LDL uptake into hepatocytes. *In vivo* studies in the various animal models showed that alirocumab's inhibitory effect on PCSK9 reduced serum LDL-C concentrations in the circulation. These findings indicate that alirocumab binds to human PCSK9 and inhibits binding of PCSK9 to LDLR and subsequent LDLR degradation, causing cell surface LDLR to increase and promoting hepatic LDL-C clearance, and consequently reducing LDL-C concentrations in the circulation.

PMDA's view:

The *in vitro* and *in vivo* studies demonstrated that alirocumab specifically bind to PCSK9 and inhibited binding of PCSK9 to LDLR. Animal models showed decreased serum LDL-C after the administration of alirocumab, and alirocumab is therefore expected to be effective for treating HC in humans.

3.R.2 Effect of alirocumab on HCV infection

The applicant's explanation:

The lipid metabolic pathway is involved in the replication and maturation processes of HCV (*Trends Endocrinol Metab*. 2010;21:33-40), and the induction of LDLR expression by HCV increases lipid uptake and thus enhances HCV genome replication. Ectopically expressed PCSK9 reduces LDLR in HCV-infected Huh-7 cells, causing RNA replication of HCV to be suppressed (*J Virol*. 2014;88:2519-2529), and the overexpression of genetically modified non-secretory cell membrane-bound PCSK9 reduced the expression of CD81 (the main component of HCV entry complex) on the hepatocyte surface (*Hepatol*. 2009;50:17-24). Furthermore, the possibility that drug-induced suppression of PCSK9 expression increases CD81 expression, and the increased CD81 expression may enhance HCV invasion of hepatocytes (*N Engl J Med.* 2012;366:2425-2426). In light of these findings, the safety pharmacology studies evaluated the effect of PCSK9 inhibition by alirocumab on CD81 expression levels and HCV proliferation in hepatocytes. In both *in vitro* and *in vivo* studies, no functional relationship was observed between PCSK9 and CD81, and alirocumab did not affect the invasion efficiency of HCV pseudo particles into hepatocytes *in vitro*. The interactions between alirocumab and LDLR did not affect the HCV replication cycle. Therefore, the inhibition of PCSK9 in the circulation by alirocumab does not enhance susceptibility to HCV infection.

PMDA's view:

In theory, the possibility that alirocumab may increase the risk of onset and aggravation of hepatitis C cannot be denied. The pharmacology studies of alirocumab did not show any effect of alirocumab on HCV infection and HCV proliferation processes, and therefore, ascribing increasing risk of HCV infection to alirocumab is premature at present. Nevertheless, the risk of HCV infection associated with alirocumab should be determined based on knowledge that will be available in the future.

3.R.3 Possibility that PCSK9 inhibition affects organs other than the liver

PCSK9 is primarily expressed in the liver but is also known to be expressed in the small intestine, kidney, pancreas, and brain (*Proc Natl Acad Sci USA*. 2003;100:928-933. *J Neurochem*. 2006;98:838-850. *Biochem Biophys Res Commun*. 2009;390:1288-1293). PMDA requested the applicant to explain how alirocumab's inhibitory effect on PCSK9 will affect the organs other than the liver.

The applicant's explanation about the effect of PCSK9 deficiency on each organ:

Small intestine: Alirocumab's inhibitory effect on PCSK9 may contribute to reducing postprandial lipid and increasing lipid excretion from blood via the small intestine, etc. However, currently there are no data showing inhibitory effects of antibodies on PCSK9 on enteral cholesterol excretion.

Kidney: Alirocumab's inhibitory effect on PCSK9 may increase amiloride-sensitive epithelial sodium channel activity, enhancing renal sodium reabsorption and thereby increasing blood pressure. However, according to a genetic study, humans with a *PCSK9* nonsense mutation (Y142X or C679X9) is less likely to have hypertension as compared with non-carriers of these genes (*N Engl J Med.* 2006;354:1264-1272). Furthermore, the available clinical data of alirocumab show no clinically significant effect of PCSK9 inhibition on blood pressure or changes in electrolyte concentrations.

Pancreas: Discussions suggest potential involvement of PCSK9 in glucose homeostasis (*J Clin Endocrinol Metab.* 2009;94:2537-2543. *Clin Chem*. 2009;55:1637-1645). On the other hand, the toxicity studies did not indicate effects of alirocumab on blood glucose control and body weight. The clinical study data show no tendency suggesting risks related to glucose metabolism and an onset of diabetes associated with alirocumab.

Brain: Studies on roles of PCSK9 in Alzheimer's disease in *PCSK9* knockout mice have not yielded consistent results (*EMBO Rep.* 2008;9:916-922. *J Lipid Res.* 2010;51:2611-2618). The past clinical studies have produced no evidence of Alzheimer's disease caused by alirocumab. Although the intracerebral *PCSK9* mRNA expression was most frequent in the cerebellum, no sign of cerebellar syndrome due to the administration of alirocumab was noted in the past clinical studies. In conclusion, no clinical study data indicate a potential inhibitory effect of alirocumab on PCSK9 expressed in the brain.

Pcsk9$^{hum/hum}$ mice received a single dose of alirocumab, then received human PCSK9 intravenously 20 hours later. A total of 8 organs (liver, brain, lung, kidney, heart, ileum, adrenal gland, and pancreas) were sampled from the animals 24 hours later to determine LDLR levels in these organs. No effect of alirocumab on LDLR levels was found in the organs other than the liver (CTD 4.2.1.1-6).

Alirocumab has been shown to inhibit free PCSK9 but there is no data showing inhibition of intracellular PCSK9 in tissues expressing PCSK9. Alirocumab is therefore considered to inhibit extracellular PCSK9 only. Furthermore, the results of the toxicity studies and clinical studies indicated that inhibition of extracellular PCSK9 by alirocumab would not affect the organs other than the liver.

PMDA's view:
PCSK9 is expressed not only in the liver but also in other organs, and may have other functions than blood LDL-C regulation. Although past non-clinical studies of alirocumab have shown no adverse effect of alirocumab in tissues expressing PCSK9, the possibility remains that alirocumab may inhibit PCSK9 expressed in the organs other than the liver. The clinical study data should be reviewed for any AEs in non-liver organs due to alirocumab's inhibitory effect on PCSK9. The clinical safety of alirocumab should be further evaluated in post-marketing surveillance and other surveys.

4. Non-clinical Pharmacokinetic Data and Outline of the Review Conducted by PMDA

Serum alirocumab concentrations were determined by ELISA, and the limit of quantification was 39 ng/mL in rats and monkeys. Serum anti-drug antibody (ADA) was determined by electrochemiluminescence (ECL), and the detection limit was 8.63 ng/mL in rats and 11.40 ng/mL in monkeys.

The pharmacokinetic (PK) parameters are shown in mean or mean ± standard deviation (SD) unless otherwise specified.

4.1 Absorption

4.1.1 Single-dose studies (CTD 4.2.2.2-1 to 2, 4.2.2.2-3, 4.2.2.7-1)

Table 5 shows the PK parameters of a single dose of alirocumab administered subcutaneously or intravenously to male and female rats and male and female monkeys.

Table 5. PK parameters of a single dose of subcutaneous or intravenous alirocumab

Animal	Route of admini-stration	Dose (mg/kg)	Sex	No.	$C_{max, s}$ (μg/mL)	t_{max}[a] (day)	AUC_{inf} (μg·day/mL)	$t_{1/2}$ (day)	V_{ss} (mL/kg)	CL[b] (mL/day/kg)	BA (%)
Rat	SC	1	Female	7	8.15 ± 1.66	3.04	59 ± 8	5.00 ± 0.717	–	17.3 ± 2.62	97.4
		5	Male	7	29.0 ± 14.0	3.04	239 ± 85	5.08 ± 1.00	–	22.6 ± 5.76	49.9
			Female	7	32.2 ± 5.57	2.04	290 ± 36	5.00 ± 0.525	–	17.5 ± 2.74	68.2
		15	Female	7	68.7 ± 12.3	3.04	642 ± 181	4.21 ± 1.25	–	25.4 ± 8.95	43.7
	IV	1	Female	7	–	–	60 ± 13	4.09 ± 0.958	85.3 ± 12.5	17.3 ± 4.13	–
		5	Male	7	–	–	495 ± 173	4.75 ± 0.979	73.9 ± 11.2	11.0 ± 3.14	–
			Female	7	–	–	424 ± 77	4.79 ± 0.596	80.3 ± 7.38	12.1 ± 2.23	–
		15	Female	7	–	–	1469 ± 277	4.63 ± 1.34	70.5 ± 11.1	10.6 ± 2.66	–
Monkey	SC	1	Male	3	10.8 ± 1.57	2.00	65 ± 11	2.11 ± 0.343	–	15.6 ± 2.83	76.1
			Female	3	11.6 ± 3.36	4.00	66 ± 12	2.16 ± 0.165	–	15.5 ± 2.78	77.0
		15	Male	3	166 ± 82.0	5.00	1931 ± 768	5.83 ± 0.729	–	8.52 ± 2.86	74.7
			Female	3	191 ± 27.3	3.00	2086 ± 372	6.38 ± 0.571	–	7.34 ± 1.31	71.7
	IV	1	Male	3	–	–	86 ± 14	2.20 ± 0.216	39.0 ± 2.95	11.9 ± 1.90	–
			Female	3	–	–	86 ± 18	2.14 ± 0.411	37.4 ± 1.78	12.0 ± 2.28	–
		3	Male	3	–	–	842 ± 436	2.68 ± 0.821	18.6 ± 4.72	4.13 ± 1.65	–
			Female	3	–	–	212 ± 11	2.41 ± 0.127	72.6 ± 26.3	14.2 ± 0.708	–
		15	Male	3	–	–	2582 ± 809	6.21 ± 1.06	–	6.17 ± 1.69	–
			Female	3	–	–	2910 ± 133	7.08 ± 1.25	–	5.16 ± 0.237	–

– Not calculated
[a] Median, [b] CL/F for subcutaneous dose

To elucidate impact of the differences in the manufacturing process of the drug substance and the concentration of the solution on the PK of alirocumab, a single dose of the drug substance 5 mg/kg (concentration of the solution, 15, 150, or 175 mg/mL) manufactured using the C1 cell line (used in the non-clinical, phase I, and phase II studies) or the C2 cell line (used in the phase III study) was subcutaneously or intravenously administered to male monkeys, and serum alirocumab concentrations were determined. The PK parameters of alirocumab are shown in Table 6.

Table 6. PK parameters of a single dose of subcutaneous or intravenous alirocumab in monkeys

Route of admini-stration	Type of cell line	Dose (mg/kg)	Concentration of solution (mg/mL)	N	$C_{max, s}$ (μg/mL)	t_{max}[a] (day)	AUC_{inf} (μg·day/mL)	$t_{1/2}$ (day)	BA (%)
SC	C1	5	150	6	40.7 ± 8.50	2.50	332 ± 50	2.59 ± 0.274	52.8
	C2	5	15	6	47.6 ± 9.11	2.00	407 ± 88	2.70 ± 0.325	–
		5	150	6	41.2 ± 11.0	3.00	346 ± 130	2.78 ± 0.588	54.6
		5	175	6	51.8 ± 6.38	2.00	450 ± 60	2.86 ± 0.320	–
IV	C1	5	150	6	–	–	629 ± 157	2.45 ± 0.398	–
	C2	5	150	6	–	–	634 ± 33	2.62 ± 0.303	–

– Not calculated
[a] Median

4.1.2 Repeated-dose studies (CTD 4.2.3.2-1 to 5, 4.2.3.2-7 to 9, 4.2.3.5.2-1)

The toxicokinetic (TK) data from the repeated-dose toxicity studies were submitted as the PK data of repeated subcutaneous doses of alirocumab.

Table 7 shows the PK parameters of alirocumab administered subcutaneously once weekly for 26 weeks to male and female rats.

Table 7. PK parameters of repeated doses of subcutaneous alirocumab in rats

Dose (mg/kg)	Sex	N	Measurement point (Week)	$C_{max, s}$ (μg/mL)	AUC_{last} (μg·day/mL)
5	Male	4	1	23.1 ± 1.69	125 ± 11
		4	25	18.8 ± 10.0	104 ± 58
	Female	4	1	24.9 ± 4.09	136 ± 20
		4	25	20.2 ± 9.35	111 ± 54
15	Male	4	1	51.8 ± 6.01	301 ± 38
		4	25	28.4 ± 22.3	166 ± 134
	Female	4	1	66.1 ± 9.88	372 ± 63
		4	25	97.4 ± 79.4	542 ± 493
50	Male	4	1	197 ± 65.2	1109 ± 409
		4	25	151 ± 55.0	877 ± 310
	Female	4	1	149 ± 18.6	865 ± 138
		4	25	219 ± 162	1451 ± 432

Table 8 shows the PK parameters of alirocumab administered subcutaneously once weekly for 26 weeks to male and female monkeys.

Table 8. PK parameters of repeated doses of subcutaneous alirocumab in monkeys

Dose (mg/kg)	Sex	N	Measurement point (Week)	$C_{max, s}$ (μg/mL)	$AUC_{0\text{-}168h}$ (μg·day/mL)
5	Male	6	1	40.3 ± 6.87	236 ± 42
		6	25	151 ± 47.7	868 ± 236
	Female	6	1	34.2 ± 5.06	189 ± 28
		6	25	88.7 ± 24.4	512 ± 133
15	Male	6	1	130 ± 28.1	745 ± 179
		6	25	430 ± 87.1	2780 ± 629
	Female	6	1	111 ± 6.65	654 ± 41
		6	25	298 ± 34.4	1865 ± 227
75	Male	6	1	640 ± 201	3683 ± 1208
		6	25	2005 ± 481	11,958 ± 3275
	Female	6	1	535 ± 103	3153 ± 612
		6	25	1633 ± 361	9694 ± 1982

Alirocumab 5, 15, or 75 mg/kg was administered subcutaneously to pregnant rats on Days 6 and 12 of gestation (9 rats/group). Fetal serum alirocumab concentrations on Day 21 of gestation were similar to those in mother rats in the 5 and 15 mg/kg groups and were approximately 3-fold those in mother rats in the 75 mg/kg group.

Alirocumab 15 or 75 mg/kg was administered subcutaneously to pregnant monkeys (20 monkeys/group) once weekly from Day 20 of gestation until delivery (approximately Day 160 of gestation). Alirocumab was detected in the serum in all newborns (14 in the 15 mg/kg group and 11 in the 75 mg/kg group) at 7 days after birth. At 90 days after birth, alirocumab was detected in the serum in 3 of 14 newborns in the 15 mg/kg group and 11 of 12 newborns in the 75 mg/kg group. Serum alirocumab concentrations decreased to BLQ by 178 days after birth in newborns in all treatment groups.

4.2 Distribution

No study was conducted for the current application.

4.3 Metabolism

No study was conducted for the current application.

4.4 Excretion

No study was conducted for the current application.

4.5 PK interactions (CTD 4.2.3.2-10 to 12)

Male and female monkeys received alirocumab (75 mg/kg, once weekly, 13 weeks, intravenous) or atorvastatin (25 or 40 mg/kg, once weekly, 13 weeks, via nasogastric tube) alone or in combination. Table 9 shows the PK parameters of alirocumab, atorvastatin, and the metabolites of atorvastatin (*o*- and *p*-hydroxy atorvastatin). The $C_{max, s}$ and AUC_{last} of alirocumab tended to decrease slightly when

combined with atorvastatin. No clear effect of alirocumab was noted on the PK of atorvastatin and its metabolites following the co-administration.

Table 9. PK parameters of alirocumab, atorvastatin, and the metabolites of atorvastatin

	N	Measurement point (Week)	C_{max}[a]	AUC_{last}[b]
Alirocumab				
Alirocumab alone	12	1	2250 ± 479	7500 ± 1250
	12	13	3270 ± 632	13,100 ± 1760
Atorvastatin 25 mg/kg + alirocumab	12	1	1920 ± 253	5630 ± 658
	12	13	3010 ± 385	11,300 ± 1650
Atorvastatin 40 mg/kg + alirocumab	12	1	1860 ± 411	5460 ± 758
	12	13	2740 ± 376	10,500 ± 1570
Atorvastatin				
Atorvastatin 25 mg/kg alone	12	1	59.0 ± 37.6	278 ± 94.8
	12	13	92.1 ± 47.3	524 ± 198
Atorvastatin 25 mg/kg + alirocumab	12	1	50.3 ± 24.7	249 ± 172
	12	13	189 ± 299	636 ± 601
Atorvastatin 40 mg/kg alone	12	1	129 ± 120	571 ± 251
	12	13	92.7 ± 62.3	845 ± 346
Atorvastatin 40 mg/kg + alirocumab	12	1	69.5 ± 38.1	405 ± 182
	12	13	126 ± 75.1	950 ± 516
o-Hydroxy atorvastatin				
Atorvastatin 25 mg/kg alone	12	1	136 ± 53.2	824 ± 163
	12	13	170 ± 73.1	700 ± 280
Atorvastatin 25 mg/kg + alirocumab	12	1	170 ± 64.4	980 ± 502
	12	13	253 ± 139	1110 ± 230
Atorvastatin 40 mg/kg alone	12	1	184 ± 114	1190 ± 824
	12	13	175 ± 136	930 ± 412
Atorvastatin 40 mg/kg + alirocumab	12	1	213 ± 83.5	1270 ± 455
	12	13	165 ± 91.1	1230 ± 671
p-Hydroxy atorvastatin				
Atorvastatin 25 mg/kg alone	12	1	6.10 ± 8.17	16.4 ± 17.5
	12	13	6.82 ± 4.13	23.1 ± 19.4
Atorvastatin 25 mg/kg + alirocumab	12	1	5.16 ± 2.48	17.8 ± 10.9
	12	13	15.0 ± 20.8	51.4 ± 40.0
Atorvastatin 40 mg/kg alone	12	1	11.9 ± 14.5	40.3 ± 38.6
	12	13	11.4 ± 15.5	76.7 ± 41.2
Atorvastatin 40 mg/kg + alirocumab	12	1	8.07 ± 3.91	46.0 ± 38.7
	12	13	7.65 ± 4.21	48.9 ± 37.8

[a] Alirocumab, μg/mL; atorvastatin and its metabolites, ng/mL
[b] Alirocumab, μg·day/mL; atorvastatin and its metabolites, ng·h/mL

4.R Outline of the review conducted by PMDA

The applicant's explanation about the distribution, metabolism, and excretion of alirocumab, which were not investigated in the studies for the current application:

Alirocumab is expected to be distributed similarly to endogenous IgG. Generally, mAb is large in molecular weight and highly water-soluble, and is therefore distributed only to extracellular fluids in blood vessels and blood flow-rich organs with high vascular permeability such as the liver and kidney

(*Clin Pharmacol Ther.* 2008;84:548-558. *AAPS J*. 2009;12:33-43. *Clin Pharmacokinet.* 2013;52:855-868. *Clin Pharmacokinet.* 2015;54:35-80). The V_{ss} of alirocumab after a single intravenous dose in rats (approximately 71-91 mL/kg) and monkeys (approximately 19-73 mL/kg) were similar to or slightly higher than the plasma volumes in rats (approximately 30-40 mL/kg) and monkeys (approximately 45 mL/kg) (*Pharm Res*. 1993;10:1093-1095. *J Appl Physiol*. 1994;76:485-489). Therefore, alirocumab is also expected to be found primarily in blood vessels and distributed from blood to limited extracellular fluids in specific organs. Alirocumab is an IgG antibody and is assumed to be catabolized into peptides and amino acids. Endogenous IgG is known to be transferred to milk in human (*Am J Gastroenterol.* 2009;104:228-233). Therefore, the possibility remains that alirocumab, for being an IgG antibody, may be transferred to milk.

Thus, considering the distribution, metabolism, and excretion of alirocumab were inferable from the existing data, no non-clinical study was conducted on these chemical processes for the current application.

PMDA's view:
Although the distribution, metabolism, and excretion of alirocumab were not investigated in a non-clinical study, the applicant's explanation that these chemical processes of alirocumab are able to be inferred from the existing knowledge is reasonable. In view of the submitted data and applicant's explanation, the non-clinical PK of alirocumab is considered to have been appropriately evaluated.

5. Toxicity and Outline of the Review Conducted by PMDA

The toxicity studies of alirocumab included repeated-dose toxicity studies, reproductive and developmental toxicity studies, and others (immunophenotype study and tissue cross-reactivity study). Because alirocumab showed high affinity to PCSK9 of humans, cynomolgus monkeys, rats, mice, and hamsters, the toxicity studies of alirocumab were conducted in rats and cynomolgus monkeys.

5.1 Single-dose toxicity

No single-dose toxicity study of alirocumab was conducted. In repeated-dose toxicity studies, however, alirocumab was administered intravenously or subcutaneously to rats and cynomolgus monkeys, and neither deaths nor signs of acute toxicity were observed after the initial dose. The applicant determined that the lethal dose was approximately >75 mg/kg in all animal species and regardless of the route of administration.

5.2 Repeated-dose toxicity

Alirocumab was administered to rats and cynomolgus monkeys intravenously or subcutaneously for up to 6 months in repeated-dose toxicity studies. In another study, alirocumab was administered to cynomolgus monkeys intravenously for up to 3 months to evaluate toxicity of alirocumab co-administered with atorvastatin. In any of these studies, no specific change was noted in the general condition, toxicity findings, immune responsiveness, and bile acid production, except for changes in

cholesterol due to the pharmacological effect of alirocumab. The applicant determined the no observed adverse effect level (NOAEL) as 50 mg/kg ($AUC_{0\text{-}2\ weeks}$, 2247 μg·day/mL) in the 6-month subcutaneous dose toxicity study in rats and 75 mg/kg ($AUC_{0\text{-}2\ weeks}$, 21,653 μg·day/mL) in the 6-month subcutaneous dose toxicity study in cynomolgus monkeys. The exposure ratios were 7.6-fold and 73-fold, respectively, as compared with the $AUC_{0\text{-}2\ weeks}$ (296 μg·day/mL) after subcutaneous doses of alirocumab 150 mg once every 2 weeks (Q2W) in Japanese HeFH or HC patients (Japanese phase II study [Study DFI12361]). Because no toxicity was found in the evaluation of local irritation in the injection site examination after intravenous and subcutaneous doses, the applicant concluded that alirocumab has no local irritant effect.

5.2.1 Two-week repeated intravenous dose toxicity in rats (CTD 4.2.3.2-1)

Alirocumab 0 (vehicle), 0.5, 5, 15, or 75 mg/kg was administered intravenously once weekly for 16 days (3 doses in total) to 15 each of male and female SD rats. Serum LDL-C, TC, and HDL-C levels decreased in all alirocumab groups, and decreased serum LDL-C, TC, and HDL-C levels were noted in the ≥15 mg/kg groups even after a 4-week recovery period. Increased ALT was noted in some of the male rats in the ≥15 mg/kg groups and female rats in the 75 mg/kg group, but it was not noted after a 4-week recovery period. In all alirocumab groups, sinusoidal cell hyperplasia and inflammation in the liver were observed. In the 0.5 mg/kg group, these changes were mild and reversible, and accompanied no relevant clinicopathological changes. They were therefore not considered toxicologically significant. Hepatic abnormalities observed in the ≥5 mg/kg groups tended to recover, but moderate hepatic abnormalities were related to the above-mentioned increased ALT. Although extramedullary hemopoiesis in the spleen was observed in all treatment groups including the control group, it was not considered as a toxic change because of no changes in erythroid parameters and its reversibility. ADA was detected in 2 of 20 rats in the 0.5 mg/kg group, 3 of 20 rats in the 15 mg/kg group, and 1 of 20 rats in the 75 mg/kg group (males and females combined). In the TK satellite groups, blood drug concentrations were determined, and ADA was detected in 1 of 8 rats (males and females combined) each in the 15 and 75 mg/kg groups. However, ADA was not considered to have affected the overall toxicity evaluation, because of sufficient alirocumab exposure confirmed in the 2 rats. Thus, the applicant determined the NOAEL as 0.5 mg/kg/week.

5.2.2 Five-week repeated subcutaneous dose toxicity in rats (CTD 4.2.3.2-2)

Alirocumab 0 (vehicle), 0.5, 5, 15, or 75 mg/kg was administered subcutaneously once weekly for 5 weeks to 15 each of male and female SD rats. Serum LDL-C, TC, and HDL-C levels decreased in a dose-dependent manner in female rats in the ≥0.5 mg/kg groups and male rats in the ≥5 mg/kg groups. These low values resolved after a 76-day recovery period in all treatment groups. Sinusoidal cell hyperplasia and inflammation in the liver were observed in 2 of 20 rats in the 5 mg/kg group, 5 of 20 rats in the 15 mg/kg group, and 11 of 20 rats in the 75 mg/kg group (males and females combined). However, these were not considered toxicity evidence because they were minimal to mild and reversible changes not related to changes in clinicopathological parameters including ALT. ADA production was evaluated in the satellite group, and it was observed in 2 of 8 rats in the 0.5 mg/kg group, 2 of 8 rats in

the 5 mg/kg group, 2 of 8 rats in the 15 mg/kg group, and 5 of 7 rats in the 75 mg/kg group (male and female combined). ADA was not considered to have affected the toxicity evaluation because of sufficient alirocumab exposure for the saturation of binding to PCSK9 at ≥15 mg/kg/week. Thus, the applicant determined the NOAEL as 75 mg/kg/week.

5.2.3 Thirteen-week repeated intravenous and subcutaneous dose toxicity in rats (CTD 4.2.3.2-3)

Alirocumab 0 (vehicle), 5, 15, or 75 mg/kg was administered intravenously once weekly for 13 weeks or 50 mg/kg subcutaneously once weekly for 13 weeks to male and female SD rats (15 each of male and female rats). Serum LDL-C, TC, and HDL-C decreased in the ≥5 mg/kg groups regardless of the route of administration, and recovered after a 16-week recovery period. Increased adrenal gland weight were noted in female rats in the 50 mg/kg group and male and female rats in the 75 mg/kg group. However, it tended to recover after recovery period without causing histopathological abnormality in the adrenal gland or affecting their general condition. These changes were therefore not considered toxicologically significant. Increased renal and hepatic weight were observed in the 50 mg/kg group. However, these changes were within the site historical data and did not accompany abnormality in the laboratory data or histopathological examination. Thus they were not considered toxicologically significant. ADA production was evaluated in the satellite group. ADA was detected in 1 of 7 rats in the 5 mg/kg group and 6 of 8 rats in the 50 mg/kg group (total number of male and female rats). The applicant considered that ADA did not affect the toxicity evaluation, because of was sufficient alirocumab exposure for the saturation of binding to PCSK9. The applicant thus determined the NOAEL as 75 mg/kg/week for the intravenous dose and 50 mg/kg/week for the subcutaneous dose.

5.2.4 Twenty-six-week repeated subcutaneous and intravenous dose toxicity in rats (CTD 4.2.3.2-4)

Alirocumab 0 (vehicle), 5, 15, or 50 mg/kg was administered subcutaneously once weekly for 26 weeks or 30 mg/kg intravenously once weekly for 26 weeks to male and female SD rats (15 each male and female rats). Increased weight gain was observed in the ≥5 mg/kg groups and increased cumulative food intake in the 50 mg/kg group, regardless of the route of administration. However, these findings were minimal changes and did not affect their general condition, and therefore not considered toxicologically significant. Serum LDL-C, TC, and HDL-C decreased in all alirocumab groups, regardless of the route of administration, but recovered after a 16-week recovery period with no rebound effect. Increased adrenal gland weight in females in the ≥30 mg/kg groups was not considered toxicologically significant, as it was reversed after recovery period and did not affect macroscopic findings, histopathological findings, and blood corticosterone concentrations. ADA production was evaluated in the satellite group. ADA was detected in 4 of 8 rats, 1 of 7 rats, and 3 of 7 rats in the subcutaneous 5, 15, and 50 mg/kg groups, respectively, and in 1 of 8 rats (males and females combined) in the intravenous group. The applicant considered that ADA did not affect the toxicity evaluation, because of sufficient alirocumab exposure for the saturation of binding to PCSK9 at ≥15 mg/kg/week. The applicant thus determined the NOAEL as 50 mg/kg/week for the subcutaneous dose and 30 mg/kg/week for the intravenous dose.

5.2.5 Two-week repeated intravenous dose toxicity in monkeys (CTD 4.2.3.2-5)

Alirocumab 0 (vehicle), 0.5, 5, 15, or 75 mg/kg was administered intravenously once weekly for 16 days (3 doses in total) to male and female cynomolgus monkeys (5 each of male and female monkeys). Serum LDL-C and TC decreased in the ≥0.5 mg/kg groups. The decreased LDL-C reached a steady state in the ≥5 mg/kg groups. Low serum LDL-C and TC were noted even after a 4week recovery period in the ≥15 mg/kg groups. A sign of gliosis was found around cerebral blood vessels in 1 of 3 female monkeys in the 75 mg/kg group. Being sporadic, minimal, and unlikely to occur during 2-week treatment, it was considered a pre-existing or incidental change. The appearance of eosinophilic substances increased in the germinal center of the spleen of animals in all alirocumab groups. This change was considered toxicologically insignificant because it was a dose-independent minimal to mild change, and a minimal change was observed in the control group as well (2 of 10 monkeys). No ADA production was observed. The applicant thus determined the NOAEL as 75 mg/kg/week.

5.2.6 Five-week repeated subcutaneous dose toxicity in monkeys (CTD 4.2.3.2-7)

Alirocumab 0 (vehicle), 0.5, 5, 15, or 75 mg/kg was administered subcutaneously once weekly for 5 weeks to male and female cynomolgus monkeys (5 each of male and female monkeys). Serum LDL-C decreased in male monkeys in the ≥0.5 mg/kg groups and female monkeys in the ≥5 mg/kg groups, and serum TC decreased in the ≥5 mg/kg groups. The decreased LDL-Cs almost reached a steady state in the ≥5 mg/kg groups. In the 75 mg/kg group, low serum LDL-C and TC were observed in all 4 monkeys (males and females combined) even after an 8-week recovery period. Although ADA was observed in 3 of 10 monkeys in the 0.5 mg/kg group, 2 of 10 monkeys in the 5 mg/kg group, 1 of 10 monkeys in the 15 mg/kg group, and 1 of 10 monkeys in the 75 mg/kg group (males and females combined), the applicant considered that ADA did not affect the toxicity evaluation because of sufficient alirocumab exposure for the saturation of binding to PCSK9. The applicant therefore determined the NOAEL as 75 mg/kg/week.

5.2.7 Thirteen-week repeated intravenous dose toxicity study in monkeys (CTD 4.2.3.2-8)

Alirocumab 0 (vehicle), 0.5, 5, 15, or 75 mg/kg was administered intravenously once weekly for 13 weeks (14 doses in total) to male and female cynomolgus monkeys (6 each of male and female monkeys). Serum LDL-C and TC decreased in all alirocumab groups but almost recovered after a 13-week recovery period. Although ADA was observed in 1 of 12 monkeys in the 0.5 mg/kg group, 1 of 12 monkeys in the 5 mg/kg group, 1 of 12 monkeys in the 75 mg/kg group, and 2 of 12 monkeys in 75 mg/kg group (male and female monkeys combined), the applicant considered that ADA did not affect the toxicity evaluation, because there was no difference in serum alirocumab concentrations between ADA-positive monkeys and ADA-negative monkeys. The applicant therefore determined the NOAEL as 75 mg/kg/week.

5.2.8 Twenty-six-week repeated subcutaneous and intravenous dose toxicity in monkeys (CTD 4.2.3.2-9)

Alirocumab 0 (vehicle), 5, 15, or 75 mg/kg was administered subcutaneously once weekly for 26 weeks or 50 mg/kg intravenously once weekly for 26 weeks to male and female cynomolgus monkeys (6 each of male and female monkeys). In all alirocumab groups, serum LDL-C and TC decreased in a dose-independent manner, and serum VLDL-C and TG also decreased. While these serobiochemical changes recovered after a 13-week recovery period in the 5 mg/kg group, the decreased LDL-C in the ≥15 mg/kg groups and decreased TC and VLDL-C in the ≥50 mg/kg groups, and decreased TG in the 75 mg/kg group showed little reversibility. In the ophthalmologic examination, a small depigmentation spot was found in the choroid/retina of one eye after treatment for approximately 6 months in the control and alirocumab 15 mg/kg groups (1 of 12 monkeys in each group). Because this abnormality was observed in the control group as well, and neither its incidence nor severity increased in a dose-dependent manner, the applicant considered that it was attributable to a spontaneous embolic event. Alirocumab did not affect the immune cell phenotyping (T cell and its subsets [helper T cell and cytotoxic T cell], B cell and NK cell). Although ADA was detected in 1 of 12 monkeys (males and females combined) in the subcutaneous 5 mg/kg group and 1 of 12 monkeys (males and females combined) in the intravenous group, the applicant concluded that ADA did not affect the toxicity evaluation in this study, because it was observed in the control group as well (2 of 12 monkeys, males and females combined) and did not affect serum alirocumab concentrations. The applicant therefore determined the NOAEL as 75 mg/kg/week for subcutaneous doses and 50 mg/kg/week for intravenous doses.

5.2.9 Five-week repeated-dose toxicity in monkeys in combination with atorvastatin (CTD 4.2.3.2-10)

Alirocumab 0 (vehicle) or 15 mg/kg (once weekly, 5 weeks, intravenously) and atorvastatin 0 (vehicle, 0.4% methylcellulose), 10, or 50 mg/kg/day (daily, via nasogastric tube) were administered alone or in combination to male and female cynomolgus monkeys (5 each of male and female monkeys). Aggravation of general condition such as diarrhea, loose stool, and mucous stool occurred in animals receiving atorvastatin 50 mg/kg/day. The treatment was interrupted on Day 8 in male monkeys and Day 7 in female monkeys, and resumed at 25 mg/kg/day on Day 13 in males and Day 12 in females. In the alirocumab + atorvastatin groups, serum LDL-C and TC decreased significantly as compared with those in animals receiving either alirocumab or atorvastatin alone. The effect of treatment on serum LDL-C and TC levels differed between male and female animals. Decreases in serum LDL-C and TC were not clearly seen in female monkeys treated with atorvastatin alone. In male monkeys treated with alirocumab, reversibility of decreased serum LDL-C and TC after an 8-week recovery period was noted only in several animals. In the atorvastatin groups, decreases in serum HDL-C were not enhanced by concomitant alirocumab, and the concentrations recovered or tended to recover after an 8-week recovery period. In the alirocumab + atorvastatin groups, serum VLDL-C decreased but recovered after an 8-week recovery period. After the administration of alirocumab, serum TG decreased and, in female monkeys, remained low even after an 8-week recovery period. Decreased albumin, total protein, and calcium were occasionally observed and were considered attributable to atorvastatin. These changes

were not enhanced by concomitant alirocumab. In the atorvastatin groups (including the vehicle group), mild bleeding in the gastrointestinal mucosa including that in the large intestine persisted even after recovery period, but bleeding was not enhanced by concomitant alirocumab. Hematuria, presumably attributable to atorvastatin or the vehicle, occurred but was not enhanced by concomitant alirocumab. ADA was detected 1 of 10 monkeys (total number of male and female monkeys) in each of the alirocumab 15 mg/kg and the alirocumab 15 mg/kg/atorvastatin 50 mg/kg groups. The applicant, however, concluded that there was no clear effect of concomitant atorvastatin on ADA production in light of its frequency. Based on these results, the applicant concluded that the toxicity of alirocumab was not enhanced additively or synergistically by the combination use with atorvastatin, and determined the NOAEL of alirocumab as 15 mg/kg/week with or without atorvastatin.

5.2.10 Thirteen-week repeated-dose toxicity in monkeys in combination with atorvastatin (CTD 4.2.3.2-11)

Alirocumab 0 (vehicle) or 15 mg/kg (once weekly, 13 weeks, intravenously) or atorvastatin 0 (vehicle, 0.4% methylcellulose), 10, or 25 mg/kg/day (daily, via nasogastric tube) was administered alone or in combination to male and female cynomolgus monkeys (6 each of male and female monkeys). In the alirocumab/atorvastatin groups, serum LDL-C, VLDL-C, TC, and TG significantly decreased as compared with the alirocumab or atorvastatin alone groups. Animals in the atorvastatin groups had decreased serum HDL-C, which was however not enhanced by concomitant alirocumab. Atorvastatin alone did not affect serum VLDL-C and TG. Animals in the atorvastatin groups had reduced globulin and total protein. These changes in serobiochemical parameters recovered after an 8-week recovery period. A histopathological examination detected decreased zymogen granules in the pancreas in all female monkeys except those in the control group. This finding was, however, considered toxicologically not significant, due to being a non-dose responsive, reversible change occurred only in one sex without changes in the general condition and gastrointestinal function. ADA was detected in 1 of 12 monkeys (males and females combined) in the control group and 2 of 12 monkeys (males and females combined) in the alirocumab (15 mg/kg)/atorvastatin (25 mg/kg/day) group, but the applicant concluded that there was no effect on the toxicity evaluation. However, the presence of ADA even before the administration of alirocumab or in animals that received the vehicle suggested interference of serum, while ADA did not affect serum alirocumab concentrations. The applicant determined the NOAEL of alirocumab was 15 mg/kg/week with or without atorvastatin.

5.2.11 Thirteen-week repeated-dose additional toxicity in monkeys in combination with atorvastatin (CTD 4.2.3.2-12)

Alirocumab 0 (vehicle) or 75 mg/kg (once weekly, 13 weeks, intravenously) or atorvastatin 0 (vehicle, 0.4% methylcellulose), 25, or 40 mg/kg/day (daily, via orogastric tube) was administered alone or in combination to male and female cynomolgus monkeys (6 each of male and female monkeys). In the atorvastatin groups, the frequency of red colored stool and liquid stool increased in a manner dependent on the atorvastatin dose, but the frequency was not increased by concomitant alirocumab. In the alirocumab + atorvastatin groups, serum LDL-C, VLDL-C, HDL-C, TC, and TG were lower than the

alirocumab or atorvastatin alone but recovered 16 weeks after recovery period. Alirocumab 75 mg/kg alone decreased HDL-C by 26% to 28% from baseline. The serum bile acid synthesis biomarker (7α-hydroxy-4-cholesten-3-one), fecal bile acid content (primary, secondary, and total bile acid), and the bile acid synthesis biomarker in hepatic tissue (7α-hydroxylase mRNA) remained unchanged after the treatment, and the applicant concluded that the treatment did not affect the bile acid production. Alirocumab affected neither the immunophenotyping of T cells (CD3+/CD4+, CD3+/CD8+) and B cells nor cytotoxic T cell activity. NK cell count (CD3−/CD16+) decreased in the alirocumab groups. This was caused by the inhibitory effect of alirocumab on the detection of NK cell antigen CD16 (see CTD 4.2.3.7.2-1), and no effect was noted on the NK cell count when CD159a antigen was used as an NK cell marker. No reduction in NK cell activity was observed. When keyhole limpet hemocyanin (KLH) was subcutaneously administered approximately 5 and 9 weeks after the start of alirocumab, no effect of alirocumab was observed in T-cell-dependent antibody response that was used to evaluate specific IgG and IgM producibility against KLH. A histopathological examination showed decreased micro vacuoles in the zona fasciculata of the adrenal cortex, which is a secondary change due to decreased serum lipid. The combination of alirocumab with atorvastatin increased severity and frequency of the change. Diffuse inflammatory cell infiltration into the hepatic portal space and intrahepatic bile duct, intrahepatic bile duct hyperplasia, and mononuclear cell infiltration into the gastrointestinal mucosa were common in monkeys treated with atorvastatin, but these changes were not intensified by the combination with alirocumab. Syncytium formation under the hepatic capsule was observed at the end of treatment in 1 of 8 monkeys (total numbers of male and female monkeys) in each combination group. These histopathological findings were either secondary adaptive changes due to decreased cholesterol or reversible changes of low severity, and thus not considered alirocumab-related toxicity. ADA was produced during recovery period in 1 of 12 monkeys (total number of male and female monkeys) in the alirocumab (75 mg/kg)/atorvastatin (40 mg/kg/day) group but did not affect serum alirocumab concentrations. The applicant therefore concluded that there was no effect of ADA on the toxicity evaluation. Accordingly, the applicant determined the NOAEL of alirocumab as 75 mg/kg/week with or without atorvastatin.

5.3 Carcinogenicity

There are not many available articles discuss the risk of tumor development due to PCSK9 inhibition, and currently none suggests a mechanism- or target-related causal relationship between PCSK9 inhibition and increased risk of tumor development. While some suggest that decreased cholesterol may inhibit the activation and growth of immune cells (*J Biol Chem.* 1986;261:3620-3627. *Atherosclerosis.* 2012;220:11-21. *J Lipid Res.* 2013;54:3106-3115. *Clin Immunol Immunopathol.* 1997;84:145-149), the effect of alirocumab on immune parameters has rarely been reported. Others report that enhanced hepatic cholesterol metabolism increases intestinal bile acid load, inducing cancer (*Mutat Res*. 2005;589:47-65. *Int J Food Sci Nutr.* 2009;60(suppl 6):116-125), but no effect of alirocumab on bile acid synthesis has been observed. Furthermore, in the repeated-dose toxicity studies in rats and monkeys, the frequency of development of neoplastic lesions and preneoplastic proliferative lesions did not increase. The applicant,

therefore, considered that long-term treatment with alirocumab would not increase the carcinogenic risk, and did not perform carcinogenicity studies in animals.

5.4 Reproductive and developmental toxicity

An embryo-fetal development study in rats and an enhanced pre- and postnatal development (ePPND) study including maternal function in cynomolgus monkeys were performed as reproductive and developmental toxicity studies. The applicant determined the NOAEL in the ePPND study as 75 mg/kg/week ($AUC_{0\text{-}2\ weeks}$, 16,992 μg·day/mL), and the exposure ratio as 57-fold the $AUC_{0\text{-}2\ weeks}$ (296 μg·day/mL) after the subcutaneous administration of alirocumab 150 mg Q2W to Japanese patients with HeFH or HC (Japanese phase II study [Study DFI12361]). In the 26-week repeated-dose toxicity study in monkeys, the fertility-related assessment did not show any effect of alirocumab on the estrous cycle in female monkeys, testicular volume, ejaculate volume, sperm motility, and total sperm count per ejaculation in male monkeys, or on the histopathological findings of major reproductive organs in male and female monkeys.

5.4.1 Embryo-fetal development in rats (CTD 4.2.3.5.2-1)

Alirocumab 0 (vehicle), 5, 15, or 75 mg/kg was administered subcutaneously to pregnant SD rats (25 rats in each group). A total of 4 of 34 rats in the 75 mg/kg group (including the TK group) died or were euthanized. The observation of general condition identified vaginal reddish discharge, ataxia, and hindlimb extension in some rats. An autopsy revealed hepatic discoloration accompanied by clarification of the lobular structure. The same changes except clarification of the lobular structure were observed in the surviving rats (1 of 34 rats) in the 75 mg/kg group. In the group, fetal death occurred, which was considered attributable to toxicity in the mother rats that died. No abnormal body weight, external abnormality, internal abnormality, or skeletal abnormality was observed in fetuses. Alirocumab detected in fetal serum samples demonstrated placental transfer of alirocumab. Based on these results, the applicant determined the NOAEL as 15 mg/kg/week for mother rats and 75 mg/kg/week for embryo-fetal development.

5.4.2 Enhanced pre- and postnatal development including maternal function in monkeys (CTD 4.2.3.5.3-1)

Alirocumab 0 (vehicle), 15, and 75 mg/kg was administered subcutaneously once weekly to pregnant cynomolgus monkeys from Day 20 of gestation until delivery (20 monkeys per group). Serum LDL-C, VLDL-C, TC, and TG decreased in a dose-dependent manner in all treatment groups including the control group, and the concentration levels recovered 180 days after delivery. No effect of treatment was noted on the embryo-fetal absorption rate, fetal death rate, external examination of offspring, observation of general condition, body weight, functional and morphological development, heart rate, ophthalmology, hematology, serobiochemistry including serum lipid, or immunophenotyping. No abnormality was noted in autopsy or histopathological findings in stillborn and liveborn monkeys. Liveborn monkeys, while suggesting sufficient exposure to alirocumab, showed no clear change in serum lipid levels. Cholesterol concentrations are low in newborn monkeys but rapidly increases with

growth. Therefore, newborns may have low responsiveness to alirocumab. In liveborns from mothers in the 15 mg/kg group, no effect was noted in T-cell-dependent antibody response to KLH antigen. In liveborns from mothers in the 75 mg/kg group, the secondary response of KLH-specific IgG was lower than in liveborns from mothers in the control group. However, the applicant did not consider the decreased IgG response was a toxicologically significant change, because the values were within the range of historical data at the site, and no immune dysfunction was indicated from the observation of general condition, clinicopathological examination, histopathological examination of lymphoid tissues, or immunophenotyping of peripheral lymphocytes. ADA was produced in 1 of 20 mother monkeys in the control group, 2 of 20 mother monkeys in each of the 15 and 75 mg/kg groups, and 1 of 12 liveborns from mothers in the 75 mg/kg group. The applicant however concluded that ADA did not affect the toxicity evaluation, because of no obvious effect on serum alirocumab concentrations. The applicant determined the NOAEL as 75 mg/kg/week for mother monkeys and their offspring.

5.5 Other toxicity studies

5.5.1 Identification of NK cells in human and cynomolgus monkey blood treated *in vitro* with alirocumab (CTD 4.2.3.7.2-1)

Blood cells sampled from cynomolgus monkeys (3 animals) or humans (2 subjects) were incubated with alirocumab 0 (vehicle), 100, 500, 1000, 2500, and 5000 μg/mL. The NK cell count was determined by flow cytometry using anti-CD16 mAb and anti-CD159a mAb. The ratio of the NK cell count to the total lymphocyte count in human blood was similar to that in the negative control, without being affected by alirocumab concentrations in any methods with anti-CD16 mAb alone, anti-CD159a mAb alone, or a combination of both antibodies. The ratio of NK cells to the total lymphocyte count in monkey blood decreased in a concentration-dependent manner with alirocumab ≥1000 μg/mL by the methods with anti-CD16 mAb alone and a combination with anti-CD16 mAb and anti-CD159a mAb, while the ratio was almost similar to that with the negative control by the method with anti-CD159a mAb alone regardless of alirocumab concentrations. The applicant concluded that anti-CD159a mAb should be used for the detection of NK cells, because the methods with anti-CD16 mAb are interfered by alirocumab.

5.5.2 Cross-reactivity study using human, monkey, and rat normal tissues (CTD 4.2.3.7.7-1)

Cross-reactivity of biotin-labeled alirocumab (0.4, 15.4, and 30.8 μg/mL) was studied in normal tissues of humans, cynomolgus monkeys, and SD rats. Cross-reactivity was observed in neurofilaments/nerve-like fibers in the epithelium of the skin, cerebrum, cerebellum, spinal cord and eyes, and neuroglial cells in the cerebrum and cerebellum. Specifically, endothelium, smooth muscle fibers, neutrophils, and mononuclear leukocytes were stained only in human tissue, hepatic Kupffer cells only in cynomolgus monkey tissue, and neuroepithelium of eyes, oocytes, and lens fibers only in SD rat tissue. The reason for the different cross-reactivity among the animal species was unknown. Other than cell membrane of neuroglial cells, nerve fibers, and neurofilament/nerve-like fibers, staining was localized to cytoplasm or cytoplasmic structure. MAbs are not expected to be cell membrane-permeable *in vivo*. The binding of alirocumab to nerve fibers and neuroglial cell membrane also occurred in the absence of *in vivo* conditions, such as the blood-brain barrier. The repeated-dose toxicity studies revealed no neurological,

macroscopic, or histopathological abnormality in any nerve tissues tested. Given these facts, the applicant concluded that the tissue cross-reactivity observed in this study had little toxicological significance.

5.R Outline of the review conducted by PMDA

5.R.1 Cross-reactivity

PMDA requested the applicant to explain the degree of specificity of the cross-reactivity and toxicological significance of the results of the cross-reactivity study.

The applicant's explanation:

Biotin-labeled alirocumab stained the positive-control substance (frozen section of human PCSK9 Sepharose-coupled beads) and auxiliary control substance (UV-resin spot slide of recombinant soluble human PCSK9) moderately to strongly. On the other hand, alirocumab did not bind to tissues of the liver, kidney, and small intestine, where PCSK9 is known to be highly expressed (*Curr Opin Lipidol*. 2015;26:155-161). This may have been attributable to the solubility of PCSK9 that does not allow itself to bind closely to cell surface. PCSK9 may have been eliminated during the preparation of immunohistochemical samples, or PCSK9 concentrations in the samples may have been below the detection limit. In humans, cynomolgus monkey, and SD rat sample tissues, staining was weak and generally infrequent. Occasionally, staining was observed only with alirocumab at a high concentration (30.8 μg/mL). These differences in the intensity and frequency of staining were considered due to relatively low expression of PCSK9 in sample tissues of humans, monkeys, and rats in contrast to the excessive expression of PCSK9 in the positive-control substance. Tissues from endothelium, smooth muscle fibers, neutrophils, mononuclear leukocytes, and several epithelial cells were stained in human tissue panels and not stained in monkey and rat panels. Even in human tissues, alirocumab at a low concentration (0.4 μg/mL) failed to stain, and staining with highly concentrated alirocumab was generally weak to moderate and sporadic. While the staining patterns of alirocumab were similar among neurofilament, nerve-like fibers, and neuroglial cells in the human, monkey, and rat tissue panels. Nevertheless, in the *in vivo*-environment, mAb is unlikely to pass easily through the blood-brain barrier. In newborns, tight junction is immature and the blood-brain barrier functions incompletely. Despite that, neurobehaviors, psycho-neurologic development, and learning capacity of newborn monkeys of up to 180 days old in the ePPND study were comprehensively assessed. The results suggested no effect of alirocumab on the relevant psycho-neurologic function and development parameters. Furthermore, a histopathological examination showed no toxic change in the brain caused by alirocumab. Based on these findings, the tissue cross-reactivity observed in the study is considered toxicologically insignificant.

PMDA's view:

The applicant's claim about the toxicological insignificance of the binding observed in the cross-reactivity study is acceptable. However, monitoring for binding in human body is difficult, and whether the binding may lead to an AE is uncertain. Binding to the nervous system is particularly observed in all

animal species, suggesting the presence of a specific target antigen. Moreover, mAbs can pass through the blood-brain barrier. Therefore, nervous system-related AEs require attention during clinical studies.

5.R.2 Effect on immune response

The ePPND study in cynomolgus monkeys showed reduced secondary response of KLH-specific IgG in monkeys born to mothers in the alirocumab group. PMDA requested the applicant to explain the effect of alirocumab on immune response.

The applicant's explanation:

In the ePPND study in cynomolgus monkeys, alirocumab decreased serum lipid related to the pharmacological effect of alirocumab in mother monkeys and reduced secondary IgG response to KLH antigen administered in liveborn monkeys. Secondary immune response to KLH was not observed in the 13-week repeated-dose toxicity study of alirocumab with atorvastatin in adult monkeys. In theory, this implies concerns over the presence of toxic substances specific to immunity developed. However, there has been no report on a drug that is specifically toxic to a developing immune system of animals including humans and does not affect immunity of adult animals (*J Immunotoxicol*. 2012;9:210-230).

A repeated-measures analysis of variance including pairwise comparison of anti-KLH immunoglobulin levels with the control was performed. Moderate to strong anti-KLH IgM response was shown in most offspring within 7 days after the first KLH immunization. No statistically significant difference in IgM values was noted between the alirocumab and control groups, and the difference in IgG values after the first KLH immunization was not evident. After the second KLH immunization, a moderate to strong IgG response against KLH was observed in most offspring. In the 75 mg/kg group, the AUC and median peak values of immunoglobulin decreased statistically significantly as compared with the control group. However, the values in all treatment groups were within the historical data of the site, and these findings were therefore not considered toxic changes. Furthermore, in the ePPND study, the overall health condition of animals was maintained, and no immune dysfunction was observed in their general condition, clinicopathological examination, histopathological examination of lymphoid tissues, and immunophenotyping of peripheral lymphocytes. The alirocumab exposure in monkeys at the dose that reduced anti-KLH IgG response in the ePPND study was much higher than the exposure in humans at the highest clinical dose. The clinical studies of alirocumab revealed no sign of alirocumab-induced infection as compared with placebo. The reduced immune response to KLH was not considered clinically significant.

PMDA's view:

Toxicity studies can provide limited knowledge, in particular, on variation in immune response among animal species or the cleanliness of the test environment isolated from infection sources. Therefore, the applicant's explanation on the effect of alirocumab on immune response in mature animals is acceptable. However, the dose-dependent effect on immune response (effect on class switching of immunoglobulin) was noted in offspring of mother animals receiving alirocumab, with its mechanism unknown. Because

of lack of experience, the effect of alirocumab on the efficacy of preventive vaccination in children and the risk of infections are unknown. Therefore, in newborns and infants born to mothers treated with alirocumab during pregnancy, the possibility of reduced secondary immune response or an immunosuppressive effect and an effect on the developing immune system cannot be ruled out. Considering the possible impact on next generation, the use of alirocumab to pregnant women should be considered only when its therapeutic benefits outweigh the risks. The possible influence of alirocumab on the immune system of newborns should be highlighted in the package insert or other written materials. The possibility of increasing risk of alirocumab-induced infections in adults should be determined in light of the occurrence of AEs in the clinical studies.

6. Summary of Biopharmaceutical Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutical studies and associated analytical methods

During the development of the product, the manufacturing process of the drug substance was changed [see "2.1.4 Development of manufacturing process (equivalence/homogeneity)"]. The clinical study data submitted for the current application contain the data from an early stage of development, i.e., a phase I study, based on the drug substance manufactured using Method C1P1, subsequent clinical studies used the drug substance manufactured using Method C1P2 on an expanded manufacturing scale, and all phase III studies used the drug substance manufactured using Method C2P1 with a different cell bank and manufacturing process. Alirocumab was provided in vials, pre-filled syringes (PFSs), or pre-filled pens (PFPs) in the clinical studies. Studies in early stages, i.e., phase I and II studies used the vial. The foreign long-term study (Study LTS11717) used the PFS, and all other phase III studies used the PFP. The dosage forms for the current application are the PFS (75 and 150 mg/mL) and PFP (75 and 150 mg/mL), which were used in the Japanese and foreign phase III studies and the foreign long-term study (Study LTS11717).

Human serum drug concentrations were determined by ELISA, and the limit of quantification was 0.078 μg/mL. Human serum ADA was determined by ECL, and the detection sensitivity was approximately 1.7 ng/mL when mouse anti-alirocumab mAb was used as the positive control, and was approximately 8.9 ng/mL when rabbit anti-alirocumab polyclonal antibody was used as the positive control. Because of a false-positive case detected in patients with high LDL-C, the detection sensitivity was calculated using an assay cut point established anew with samples from subjects of Study EFC11569. The recalculated detection sensitivity was approximately 5.6 ng/mL and 22.4 ng/mL, respectively. Human serum anti-alirocumab neutralizing antibody levels were determined by ECL. The detection sensitivity was approximately 470 ng/mL when mouse anti-alirocumab mAb was used as the positive control and approximately 626 ng/mL when rabbit anti-alirocumab polyclonal antibody was used as the positive control.

6.1.1 Effect of difference in concentration of the administration solution on the PK of alirocumab (Study PKD12010, CTD 5.3.1.2-2)

A randomized, double-blind, parallel-group comparison study was conducted in 24 healthy non-Japanese adults to evaluate the effect of concentrations of the administration solution on the PK and pharmacodynamics (PD) of alirocumab after a single subcutaneous dose of alirocumab 200 mg using the 2 vial formulations with different alirocumab concentrations (175 and 150 mg/mL). Both formulations were made from the C1 cell strain-derived drug substance.

The geometric mean ratios (GMRs) of $C_{max, s}$ and AUC_{inf} of alirocumab of the 175 mg/mL formulation to those of the 150 mg/mL formulation (90% confidence interval [CI]) were 0.95 (0.79, 1.15) and 0.92 (0.78, 1.09), respectively.

Serum LDL-C levels in both treatment groups were lowest on Day 15, and the maximum reduction rates (mean ± SD) from baseline of serum LDL-C levels were 57.0 ± 14.4% (175 mg/mL formulation) and 53.6 ± 12.4% (150 mg/mL formulation). In both treatment groups, serum LDL-C levels remained ≥40% lower than the baseline values until Day 29, and nearly recovered to the baseline values by the end of the study (Day 85).

6.1.2 Effect of difference in the manufacturing method of the drug substance on the PK of alirocumab (Study PKD12011, CTD 5.3.1.2-3)

A randomized, double-blind, parallel-group comparison study was conducted in 24 healthy non-Japanese adults to compare the PK and PD of alirocumab after a single subcutaneous dose of alirocumab 200 mg using the 2 vial formulations manufactured from the drug substance prepared by Method C1P2 and C2P1 (“Formulation C1” and “Formulation C2”, respectively; alirocumab concentration, 175 mg/mL in both formulations).

The GMRs of $C_{max, s}$ and AUC_{inf} of alirocumab of Formulation C2 to those of Formulation C1 [90% CI] were 1.02 [0.85, 1.22] and 1.00 [0.81, 1.23], respectively.

Serum LDL-C of Formulations C1 and C2 were lowest on Day 11 and Day 22, respectively, and the maximum reduction rates (mean ± SD) from baseline LDL-C were 52.1 ± 14.5% and 56.1 ± 12.3%, respectively. In both treatment groups, serum LDL-C remained ≥40% lower than baseline until Day 29, and nearly recovered to the baseline values by the end of the study (Day 85).

6.1.3 Effect of difference in the volume of administration solution and the number of doses on the PK of alirocumab (Study PKD12275, CTD 5.3.1.2-4)

A randomized, open-label, parallel-group comparison study was conducted in 36 healthy non-Japanese adults to compare the PK and PD of alirocumab after subcutaneous doses of alirocumab 300 mg using the 2 vial formulations (150 and 175 mg/mL) made from the drug substance prepared by Method C2P1. A single dose of alirocumab was administered: (a) 2 mL of the 150 mg/mL formulation to 1 site, (b)

1.71 mL of the 175 mg/mL formulation to 1 site, and (c) 1 mL of 150 mg/mL formulation (per site) to 2 sites.

The GMRs of $C_{max, s}$ and AUC_{inf} of alirocumab after Method (a) to those after Method (c) (90% CI) were 0.98 (0.79, 1.21) and 0.80 (0.63, 1.02), respectively. The GMRs of $C_{max, s}$ and AUC_{inf} of alirocumab after Method (b) to those after Method (c) (90% CI) were 1.07 80.86, 1.33) and 0.96 (0.76, 1.22), respectively.

Serum LDL-C levels after Methods (a), (b), and (c) were lowest on Day 15, Day 22, and Day 15, respectively. The maximum reduction rates (mean ± SD) from baseline were 59.5 ± 11.6%, 54.3 ± 10.8%, and 52.6 ± 13.8%, respectively. In all treatment groups, serum LDL-C remained ≥40% lower than baseline until Day 29 or 43 and nearly recovered to the baseline levels by the end of the study (Day 85).

6.1.4 Effect of difference in the injection site on the PK of alirocumab (Study BDR13362, CTD 5.3.1.2-1)

A randomized, open-label, parallel-group comparison study was conducted in 60 healthy non-Japanese adults for the comparison of the PK and PD of alirocumab after a single subcutaneous dose of alirocumab 75 mg between different administration sites (abdomen, upper arm, and femoral area).

The GMRs of $C_{max, s}$ and AUC_{inf} of alirocumab administered by brachial injection to those by abdominal injection [90% CI] were 0.79 [0.66, 0.93] and 0.92 [0.78, 1.09], respectively. The GMRs of $C_{max, s}$ and AUC_{inf} of alirocumab administered by brachial injection to those by femoral injection [90% CI] were 0.90 [0.76, 1.06] and 1.09 [0.93, 1.28], respectively. The GMRs of $C_{max, s}$ and AUC_{inf} of alirocumab administered by femoral injection to those by abdominal injection [90% CI] were 0.88 [0.74, 1.04] and 0.84 [0.72, 0.99], respectively.

The reduction rates (mean ± SD) from baseline in serum LDL-C following abdominal, brachial, and femoral injections at Day 15 were 48.4 ± 15.7%, 39.5 ± 9.2%, and 45.6 ± 13.3%, respectively. The reduction rate after brachial injection tended to be lower than that after abdominal and femoral injection, but the difference was insignificant.

6.2 Clinical pharmacology

The PK parameters are shown in mean ± SD unless otherwise specified.

6.2.1 Studies in healthy adult subjects

6.2.1.1 Single subcutaneous-dose study in Japanese subjects (Study TDU12190, CTD 5.3.3.1-1)

Table 10 shows the PK parameters of alirocumab after a single subcutaneous dose of alirocumab 100, 150, 250, and 300 mg in 24 Japanese healthy adult volunteers.

Table 10. PK parameters after a single subcutaneous dose of alirocumab

Dose (mg)	N	t_{max}[a] (day)	$C_{max, s}$ (μg/mL)	AUC_{last} (μg·day/mL)	$t_{1/2}$ (day)
100	6	5.02	7.44 ± 1.68	121 ± 27.9	5.93 ± 0.437
150	6	7	6.71 ± 2.37	137 ± 61.1	7.15 ± 1.11
250	6	7	17.8 ± 5.15	368 ± 123	7.10 ± 1.05
300	6	7	29.3 ± 8.19	673 ± 142	7.55 ± 1.04

[a] Median

The maximum reduction rates from baseline serum LDL-C levels in the 100, 150, 250, and 300 mg groups were 55.4 ± 7.4%, 46.0 ± 13.0%, 60.3 ± 11.2%, and 59.8 ± 8.2%, respectively.

ADA level was determined in the 24 subjects in the alirocumab groups, A total of 2 of 6 subjects in the 100g group, 1 of 6 subjects in the 150 mg group, and 1 of 6 subjects in the 300 mg group were ADA-positive. Neutralizing antibody expression was not evaluated.

6.2.1.2 Single intravenous-dose study in non-Japanese subjects (Study CL-0902, CTD 5.3.3.1-2)

Table 11 shows the PK parameters of alirocumab after a single dose of alirocumab 0.3, 1, 3, 6, and 12 mg/kg administered intravenously over 1 hour to 30 non-Japanese healthy adults.

Table 11. PK parameters after a single intravenous dose of alirocumab

Dose (mg/kg)	N	t_{max}[a] (day)	$C_{max, s}$ (μg/mL)	AUC_{last} (μg·day/mL)	$t_{1/2}$ (day)	CL (mL/day/kg)	V_{ss} (mL/kg)
0.3	5	0.0417	8.66 ± 0.989	47.9 ± 6.84	4.75 ± 0.736	6.2 ± 0.829	38.8 ± 4.94
1	5	0.0833	27.0 ± 2.24	194 ± 23.0	5.10 ± 1.23	5.16 ± 0.612	41.5 ± 5.19
3	6	0.0833	100 ± 20.4	939 ± 179	7.97 ± 3.11	3.29 ± 0.692	39.9 ± 6.66
6	6	0.0417	172 ± 19.5	1932 ± 239	6.71 ± 0.984	3.14 ± 0.382	54.5 ± 6.78
12	6	0.0417	331 ± 48.4	4368 ± 941	6.66 ± 1.17[b]	3.17 ± 0.453[b]	54.5 ± 9.38[b]

[a] Median
[b] 4 subjects

ADA level was determined in the 30 subjects in the alirocumab groups. A total of 2 of 5 subjects in the 1 mg/kg group were ADA-positive. Expression of neutralizing antibody was not evaluated.

6.2.1.3 Single subcutaneous-dose study in non-Japanese subjects (Study CL-0904, CTD 5.3.3.1-3)

Table 12 shows the PK parameters of alirocumab after a single dose of alirocumab 50, 100, 150, and 250 mg administered subcutaneously in 24 non-Japanese healthy adults.

Table 12. PK parameters after a single subcutaneous dose of alirocumab

Dose (mg)	N	t_{max}[a] (day)	$C_{max, s}$ (μg/mL)	AUC_{last} (μg·day/mL)	$t_{1/2}$ (day)
50	6	5	5.27 ± 1.80	75.7 ± 22.0	6.33 ± 1.18
100	6	6.99	8.28 ± 3.69	131 ± 53.6	5.58 ± 0.623
150	5	7	14.6 ± 7.95	288 ± 169	7.61 ± 1.98
250	6	4.99	25.2 ± 10.4	515 ± 256	5.94 ± 1.11

[a] Median

Although the maximum serum total PCSK9 concentrations increased with the dose of alirocumab, small difference between 150 mg and 250 mg and the data suggested that binding of alirocumab to PCSK9 reaches saturation at approximately 250 mg. The maximum reduction rates from baseline serum LDL-C levels in the 50, 100, 150, and 250 mg groups were 39.8 ± 11.7%, 51.5 ± 18.2%, 57.7 ± 8.2%, and 57.8 ± 10.1%, respectively.

ADA levels were determined in the 24 subjects in the alirocumab groups. A total of 2 of 6 subjects in the 50 mg group, 1 of 5 subjects in the 150 mg group, and 4 of 6 subjects in the 250 mg group were ADA-positive. Neutralizing antibody expression was not evaluated.

6.2.2 Studies in patients

6.2.2.1 Phase II study in Japanese patients with primary HC (Study DFI12361, CTD 5.3.5.1-1)

Alirocumab 50, 75, or 150 mg was administered subcutaneously every 2 weeks (Q2W) for 12 weeks in 75 Japanese patients with primary HC receiving a stable dose of atorvastatin (5-20 mg). Table 13 shows trough serum alirocumab concentrations during the combination therapy. The trough serum alirocumab concentrations increased slightly more than dose-proportionally. The data suggested that the trough serum alirocumab concentration reaches a steady state after the second or third dose.

Table 13. Trough serum alirocumab concentrations of after repeated subcutaneous doses (μg/mL)

Dose (mg)	Week 2	Week 4	Week 6	Week 12
50	2.10 ± 1.21 (n = 25)	2.54 ± 1.61 (n = 25)	2.63 ± 1.59 (n = 25)	2.82 ± 1.99 (n = 25)
75	3.08 ± 1.57 (n = 25)	3.41 ± 1.91 (n = 25)	3.67 ± 1.71 (n = 25)	4.07 ± 2.45 (n = 25)
150	8.39 ± 4.62 (n = 25)	11.69 ± 5.31 (n = 24)	13.53 ± 8.66 (n = 23)	15.97 ± 10.96 (n = 23)

Serum total PCSK9 concentrations increased with the dose of alirocumab and were generally stable after the second dose of alirocumab. Serum concentrations of free PCSK9 decreased with the dose of alirocumab.

ADA levels were determined in the 75 subjects in the alirocumab groups. One of 25 subjects in the 50 group, 4 of 25 subjects in the 75 mg group, and 3 of 25 subjects in the 150 mg group were ADA-positive. A neutralizing antibody was detected in 1 of the 3 subjects in the 150 mg group.

6.2.2.2 Phase III study in Japanese patients with HeFH and those with HC at high risk of cardiovascular events (Study EFC13672, CTD 5.3.5.1-5)

Alirocumab 75 mg were administered subcutaneously Q2W for 24 weeks in combination with a statin to HeFH patients and HC patients at high risk of cardiovascular events. A total of 143 patients were treated for the evaluation of serum alirocumab concentrations. For patients whose serum LDL-C level at Week 8 of treatment was not lower than the prespecified value, alirocumab was increased to 150 mg from Week 12.

Trough serum alirocumab concentrations at Weeks 4, 8, 12, and 24 in 138 subjects who did not undergo dose increase were 5.31 ± 2.43, 6.32 ± 3.45, 6.77 ± 3.99, and 7.56 ± 4.58 μg/mL, respectively, and the concentrations reached a steady state after the second dose in most subjects. In 2 subjects who underwent dose increase, trough serum alirocumab concentrations at Weeks 12 and 24 were 17.00 and 45.65 μg/mL, respectively.

Serum free PCSK9 concentrations (baseline, 275.5 ± 104.9 ng/mL) in subjects who did not undergo dose increase decreased to 71.8 ± 110.6 ng/mL at Week 4 and to 46.7 ± 83.4 ng/mL at Week 24. Serum total PCSK9 concentrations (baseline, 692.1 ± 267.2 ng/mL) increased to 3734.5 ± 1028.2 ng/mL at Week 4, and remained steady (3749.3-3867.3 ng/mL) until Weeks 8 to 24. Serum free PCSK9 concentrations in subjects who underwent dose increase were BLQ until Weeks 4 to 24, and serum total PCSK9 concentrations tended to increase with increases in the alirocumab dose.

ADA levels were determined in 4 of 143 subjects in the alirocumab group and 1 of 72 subjects in the placebo group. No neutralizing antibody was detected in these subjects.

6.2.2.3 Phase I study in non-Japanese patients with HC (Study CL-1001, CTD 5.3.3.2-1)

Serum alirocumab concentrations were evaluated after subcutaneous doses of alirocumab to non-Japanese patients with FH or non-FH patients receiving a stable dose of atorvastatin (10-40 mg) or non-FH patients not receiving lipid-lowering therapy. To FH or non-FH patients treated with atorvastatin, alirocumab 50, 100, and 150 mg were subcutaneously administered on Days 1, 29, and 43, and 200 mg subcutaneously on Days 1 and 29. To non-FH patients not receiving lipid-lowering therapy, alirocumab 150 mg was subcutaneously administered on Days 1, 29, and 43.

Table 14 shows the PK parameters of alirocumab after the first dose. No clear difference was found in the PK parameters of alirocumab between FH and non-FH patients. Non-FH patients receiving alirocumab 150 mg in combination with atorvastatin tended to have lower alirocumab exposure ($C_{max,\ s}$ and AUC_{last}) than in non-FH patients receiving alirocumab alone. Exposure ($C_{max,\ p}$ and AUC) to atorvastatin and its metabolites (2- or 4-hydroxy atorvastatin) increased slightly both in the alirocumab and placebo groups, and the degree of increase was similar between the alirocumab groups and the placebo group. The exposure of neither atorvastatin nor its metabolites increased with increasing dose of alirocumab.

Table 14. PK parameters of alirocumab after the first dose

Patients	Use of atorvastatin	Alirocumab dose (mg)	N	t_{max}[a] (day)	$C_{max, s}$ (μg/mL)	AUC_{last} (μg·day/mL)	$t_{1/2}$ (day)
FH	Used	50	5	5.07	3.71 ± 1.33	47.9 ± 13.2	6.69 ± 3.03
		100	5	5.03	8.78 ± 4.96	126 ± 75.6	5.96 ± 0.687[b]
		150	5	5.09	14.4 ± 5.10	224 ± 98.4	7.82 ± 2.74
		200	3	5.14	19.6 ± 6.32	345 ± 121	8.16[c]
non-FH	Used	50	7	4.04	4.45 ± 2.11	51.8 ± 19.5	6.14 ± 1.55
		100	8	4.98	7.64 ± 1.50	114 ± 30.4	6.12 ± 0.799[d]
		150	8	4.05	10.5 ± 4.78	153 ± 71.1	6.58 ± 2.41[d]
		200	4	6.96	16.7 ± 5.36	270 ± 94.9	6.68 ± 1.30[e]
	Not used	150	8	5.04	14.0 ± 5.69	252 ± 129	7.38 ± 1.46[f]

[a] Median; [b] 4 subjects; [c] 1 subject; [d] 7 subjects; [e] 3 subjects; [f] 6 subjects

After the first dose of alirocumab, serum LDL-C levels were lowest on Day 8 or 15, and the maximum reduction rates from baseline serum LDL-C of FH patients in the 50, 100, 150, and 200 mg groups were 31.4 ± 18.2%, 53.7 ± 12.1%, 53.0 ± 17.1%, and 54.6 ± 15.4%, respectively; those of non-FH patients in the 50, 100, 150, and 200 mg groups were 43.1 ± 6.4%, 57.0 ± 19.0%, 62.0 ± 16.5%, and 55.3 ± 17.4%, respectively. The serum LDL-C lowering effect of alirocumab was similar between FH patients and non-FH patients. The maximum serum total PCSK9 concentrations tended to increase with increasing alirocumab dose, but the difference between the 150 mg and 200 mg groups was small.

Alirocumab 150 mg was administered alone or in combination with atorvastatin to non-FH patients. The maximum serum LDL-C reduction rate from baseline (on Day 15 in both groups) was higher in the alirocumab/atorvastatin group (62.0 ± 16.5%) than in the alirocumab alone group (44.7 ± 15.5%). The serum LDL-C reduction rate from baseline on Day 29 was 38.6 ± 14.3% in the alirocumab alone group and 17.6 ± 14.1% in the alirocumab + atorvastatin group. The duration of serum LDL-C lowering effect of alirocumab tended to be shorter in the alirocumab + atorvastatin group.

In FH patients, 5 of 5 subjects in the 100 mg group and 1 of 3 subjects in the 100 mg group were ADA-positive. In non-FH patients, 3 of 7 subjects in the 50 mg group, 1 of 8 subjects in the 100 mg group, and 5 of 16 subjects in the 150 mg group were ADA-positive.

6.2.2.4 Phase II study in non-Japanese patients with primary HC (Study DFI11565, CTD 5.3.5.1-3)

Table 15 shows trough serum concentrations of subcutaneous alirocumab 50, 100, and 150 mg Q2W, or 200 and 300 mg every 4 weeks (Q4W) for 12 weeks in 152 non-Japanese patients with primary HC treated with a stable dose of atorvastatin (10-40 mg). When alirocumab was administered Q2W, trough serum concentrations of alirocumab reached a steady state after the third or fourth dose.

Table 15. Trough serum concentrations of multiple doses of subcutaneous alirocumab (μg/mL)

Dose interval	Dose (mg)	Week 2	Week 4	Week 6	Week 8	Week 12
Q2W	50	1.36 ± 0.73 (N = 30)	1.54 ± 0.94 (N = 29)	1.49 ± 0.80 (N = 28)	1.64 ± 1.06 (N = 29)	1.71 ± 1.04 (N = 29)
	100	2.84 ± 1.86 (N = 31)	3.41 ± 2.52 (N = 31)	4.07 ± 3.14 (N = 31)	4.29 ± 3.21 (N = 30)	4.49 ± 3.73 (N = 30)
	150	5.65 ± 3.04 (N = 29)	7.07 ± 4.51 (N = 29)	8.62 ± 5.67 (N = 29)	9.59 ± 6.13 (N = 28)	10.64 ± 7.85 (N = 27)
Q4W	200	–	2.50 ± 4.08 (N = 26)	–	2.41 ± 4.63 (N = 25)	1.77 ± 1.34 (N = 24)
	300	–	2.26 ± 1.73 (N = 27)	–	3.25 ± 3.28 (N = 24)	3.84 ± 3.95 (N = 25)

– Not applicable

Serum concentrations of free PCSK9 decreased significantly from baseline after the administration of alirocumab in the 150 mg Q2W, 200 mg Q4W, and 300 mg Q4W groups. In the Q4W groups, the serum free PCSK9 concentration lowering effect did not last 4 weeks.

ADA levels were determined in 148 subjects in the alirocumab groups and 30 subjects in the placebo group. The number of ADA-positive subjects were 17 of 30 in the 50 mg Q2W group, 11 of 31 in the 100 mg Q2W group, 7 of 30 in the 150 mg Q2W group; 5 of 29 in the 200 mg Q4W group, 4 of 28 in the 300 mg Q4W group, and 1 of 30 in the placebo group.

6.2.2.5 Phase II study in non-Japanese patients with HeFH (Study CL-1003, CTD 5.3.5.1-4)

Table 16 shows trough serum concentrations of multiple doses of subcutaneous alirocumab 150 mg Q2W or 150, 200, and 300 mg Q4W, administered in combination with a statin to 77 non-Japanese HeFH patients treated with a stable dose of statin.

Table 16. Trough serum concentrations of multiple dose of subcutaneous alirocumab (μg/mL)

Dose interval	Dose (mg)	Week 2	Week 4	Week 6	Week 8	Week 12
Q2W	150	5.50 ± 4.40 (N = 16)	7.21 ± 6.23 (N = 16)	8.27 ± 7.91 (N = 16)	8.84 ± 9.41 (N = 16)	8.94 ± 10.4 (N = 16)
Q4W	150	–	1.07 ± 0.98 (N = 15)	–	1.47 ± 2.12 (N = 15)	1.58 ± 2.40 (N = 15)
	200	–	1.61 ± 0.96 (N = 16)	–	1.79 ± 1.54 (N = 16)	1.92 ± 1.59 (N = 16)
	300	–	5.93 ± 6.74 (N = 14)	–	6.68 ± 5.66 (N = 14)	8.15 ± 9.70 (N = 14)

– Not applicable

Further, multiple doses of alirocumab was administered to 30 patients treated with rosuvastatin to compare plasma rosuvastatin concentrations after the co-administration of alirocumab and rosuvastatin (Week 4, 12, and 20) with baseline values. No clear effect of alirocumab was observed on the PK of rosuvastatin.

The serum free PCSK9 concentrations and serum LDL-C lowering effects of alirocumab were greatest in the 150 mg Q2W group. In the Q4W groups, the serum LDL-C lowering effect was similar to that in the 150 mg Q2W group but did not last 4 weeks.

ADA levels were determined in 62 subjects in the alirocumab groups and 15 subjects in the placebo group. The number of ADA-positive subjects were 4 of 16 in the 150 mg Q2W group, 5 of 15 in the 150 mg Q4W group, 7 of 16 in the 200 mg Q4W group, and 6 of 15 in the 300 mg Q4W groups.

6.2.2.6 Phase II study in non-Japanese patients with primary HC (Study DFI11566, CTD 5.3.5.1-2)

Table 17 shows the PK parameters of multiple doses of subcutaneous alirocumab 150 mg administered Q2W for 8 weeks in combination with atorvastatin (10 or 80 mg) to 61 non-Japanese patients with primary HC treated with atorvastatin (10 mg). Trough serum concentrations of alirocumab were similar regardless of the atorvastatin dose.

Table 17. Trough serum concentrations of alirocumab co-administered with atorvastatin (μg/mL)

Concomitant drug	Week 2	Week 4	Week 6	Week 8
Atorvastatin 10 mg	5.30 ± 3.15 (N = 30)	7.76 ± 4.86 (N = 27)	8.23 ± 5.03 (N = 27)	8.72 ± 5.74 (N = 28)
Atorvastatin 80 mg	4.96 ± 2.97 (N = 29)	7.99 ± 4.96 (N = 28)	8.39 ± 5.31 (N = 28)	9.27 ± 6.62 (N = 28)

The serum LDL-C reduction rates from baseline at Week 8 were 66.7 ± 12.5% in the atorvastatin 10 mg group and 72.3 ± 14.4% in the atorvastatin 80 mg group, showing similarity between the 2 atorvastatin dose groups. No clear difference was noted also in serum concentrations of free PCSK9 or serum total PCSK9 concentrations between the groups.

The number of ADA-positive subjects were 23 of 61 subjects in the alirocumab groups and 2 of 30 subjects in the placebo group.

6.2.2.7 Phase III study in non-Japanese patients with HeFH (Study EFC12492, CTD 5.3.5.1-8)

Multiple doses of alirocumab 75 mg were subcutaneously administered Q2W in combination with a statin to 323 non-Japanese HeFH patients to evaluate serum alirocumab concentrations. For patients whose Week 8 serum LDL-C level was ≥70 mg/dL, the alirocumab dose was increased to 150 mg from Week 12. Table 18 shows trough serum concentrations of alirocumab in subjects with or without dose increase.

Table 18. Trough serum concentrations of alirocumab in subjects with and without dose increase (μg/mL)

	Week 12	Week 16	Week 24
Subjects without dose increase	4.40 ± 2.69 (N = 154)	5.16 ± 3.19 (N = 113)	4.47 ± 2.47 (N = 146)
Subjects with dose increase	4.20 ± 3.27 (N = 121)	10.64 ± 7.64 (N = 80)	12.15 ± 8.91 (N = 113)

Serum concentrations of free PCSK9 decreased after the administration of alirocumab in both subjects who did and did not undergo dose increase. The concentrations in both patient groups changed over time within a similar range of values until 12 weeks after administration. In subjects experienced dose increase, serum PCSK9 concentrations decreased further after the dose increase of alirocumab.

ADA level was determined in 307 subjects in the alirocumab group and 157 subjects in the placebo group. The number of ADA-positive subjects were 16 subjects in the alirocumab groups. A neutralizing antibody was detected in 1 of these 16 subjects

6.2.2.8 Phase III study in non-Japanese patients with HC (Study EFC11569, CTD 5.3.5.1-7)

Alirocumab 75 mg was subcutaneously administered Q2W in combination with a statin to 479 non-Japanese HC patients at high risk of cardiovascular events to evaluate serum alirocumab concentrations. Alirocumab was increased to 150 mg from Week 12 for patients who had Week 8 serum LDL-C level not lower than the prespecified value. Table 19 shows trough serum concentrations of alirocumab in subjects who did and did not undergo dose increase.

Table 19. Trough serum concentrations of alirocumab in subjects with or without dose increase (μg/mL)

	Week 12	Week 16	Week 24
Subjects without dose increase	3.69 ± 2.57 (N = 324)	4.12 ± 2.34 (N = 225)	3.95 ± 2.73 (N = 313)
Subjects with dose increase	2.79 ± 3.03 (N = 68)	7.47 ± 7.49 (N = 40)	8.38 ± 10.9 (N = 62)

In subjects who did not undergo dose increase, serum concentrations of free PCSK9 decreased from Week 4 and remained low thereafter. The serum PCSK9 lowering effect of alirocumab 75 mg Q2W tended to be weaker in subjects who underwent dose increase than in those who did not. However, in subjects experienced dose increase of alirocumab to 150 mg, both serum concentrations of free PCSK9 and LDL-C were lower than before dose increase. Changes in serum concentrations of free PCSK9 from Week 24 in subjects who underwent dose increase were similar to those in subjects who did not undergo dose increase.

ADA level was determined in 454 subjects in the alirocumab groups. A total of 22 subjects were ADA-positive, and a neutralizing antibody was detected in 7 of these 22 subjects.

6.2.3 Population analysis

6.2.3.1 Population pharmacokinetic analysis (CTD 5.3.3.5-1)

A population pharmacokinetic (PPK) analysis was performed using serum alirocumab concentration data of 296 subjects at 2340 time points from the foreign phase I studies (Studies CL0902 and CL0904) and Japanese phase I study (Study TDU12190) in healthy adults, and Japanese phase II study (Study DFI12361) and Japanese phase III study (Study EFC13672) in patients with HC. The PK of alirocumab was described by a 2-compartment model with the first-order absorption process hypothesizing linear and non-linear elimination from the central compartment.

Candidate covariates for PK parameters (CL, V2, V3, K_m, BA) were sex, age, ethnicity, body weight, BMI, Cockcroft-Gault-estimated creatinine clearance, MDRD-estimated glomerular filtration rate, albumin concentration, use of a concomitant lipid-lowering therapy, FH or non-FH status, total PCSK9 concentrations at baseline and during the study, free PCSK9 concentrations at baseline and during the study, ADA expression, use of concomitant fibrates, use of concomitant ezetimibe, use of concomitant statins, and dosage form (PFS or PFP). Body weight and free PCSK9 concentration during the study were selected as covariates significantly affecting CL. No other factors were selected as covariates for any other PK parameters.

The mean population parameters in the final PPK model were as follows: CL, 0.00685 L/h; V2, 3.08 L; V3, 1.16 L; K_a, 0.0118 h^{-1} BA, 0.53. Inter-individual variability of CL, V2, V3, K_a, and BA was 29.5%, 19.7%, 35.9%, 46.0%, and 63.2%, respectively.

6.2.3.2 PPK/PD analysis (CTD 5.3.3.5-2, 5.3.3.5-3)

A PPK/PD analysis was performed using serum alirocumab concentrations of 13,717 samples and serum LDL-C levels of 14,346 samples from 2799 subjects enrolled in the foreign phase I studies (Studies CL0902, CL0904, and PKD12910) and Japanese phase I study (Study TDU12190) in healthy adults; foreign phase II studies (Studies CL-1003, DFI11565, and DFI11566) and Japanese phase II study (Study DFI12361) in HC patients; and foreign phase III studies (Studies EFC11716, EFC11569, EFC12492, and LTS11717) in HC patients. The PK of alirocumab was described by a 2-compartment model with the first-order absorption process hypothesizing linear and non-linear elimination from the central compartment. The PK/PD model of alirocumab was described by an indirect response model, and the model parameters were K_{out}, E_{max}, EC_{50}, and Hill coefficient.

Candidate covariates for PK parameters (CL, V2, V3, K_m, BA) were sex, age, ethnicity, body weight, BMI, Cockcroft-Gault-estimated creatinine clearance, MDRD-estimated glomerular filtration rate as determined by the equation, albumin concentration, use of concomitant lipid-lowering therapy, FH or non-FH status, baseline total PCSK9 concentration, baseline free PCSK9 concentration, total PCSK9 concentration during the study, free PCSK9 concentration during the study, ADA expression, use of concomitant fibrates, use of concomitant ezetimibe, use of a concomitant statin, use of a concomitant low-dose statin, use of a concomitant high-dose statin, dosage form (PFS or PFP), and injection site (upper arm, abdomen, or thigh). Body weight and use of a concomitant statin were selected as covariates significantly affecting CL, free PCSK9 concentration during the study as a covariate significantly affecting K_m, and age as a covariate significantly affecting V3. None were selected as covariates for V2 or F (BA). The mean population parameters in the final PPK model were as follows: CL, 0.0124 L/h; V2, 3.19 L; V3, 2.79 L; K_m, 7.73 mg/L; BA, 0.862. Inter-individual variability of CL, V2, V3, K_m, and BA was 48%, 77%, 27%, 55%, and 103%, respectively.

Candidate covariates for PD parameters (K_{out}, E_{max}, EC_{50}, Hill coefficient) were disease status (healthy subjects or patients), sex, age, body weight, BMI, baseline serum LDL-C, baseline total PCSK9 concentration, baseline free PCSK9 concentration, total PCSK9 concentration during the study, free PCSK9 concentration during the study, albumin concentration, use of concomitant lipid-lowering therapy, use of concomitant fibrates, use of concomitant ezetimibe, use of a concomitant statin, use of a concomitant low-dose statin, and use of a concomitant high-dose statin. Disease status was selected as a covariate significantly affecting K_{out}, total PCSK9 concentration during the study, sex, age, body weight, baseline free PCSK9 concentration, and use of a concomitant statin as covariates significantly affecting E_{max}, baseline total PCSK9 concentration and use of a concomitant high-dose statin as covariates significantly affecting EC_{50}, and baseline free PCSK9 concentration as a covariate significantly affecting Hill coefficient.

6.2.4 Intrinsic factors

6.2.4.1 Study in patients with hepatic impairment (Study POP12671, CTD 5.3.3.3-1)

A single subcutaneous dose of alirocumab 75 mg was administered to non-Japanese subjects with normal liver function, mild hepatic impairment (Child Pugh Class A), and moderate hepatic impairment (Child Pugh Class B) (8 subjects each). The ratios of the least mean square (LMS) of $C_{max,\,s}$ of alirocumab in subjects with mild and moderate hepatic impairment to that in subjects with normal liver function (90% CI) were 1.04 (0.74, 1.48) and 0.90 (0.64, 1.26), respectively, and the ratios of LMS of AUC_{last} (90% CI) were 0.91 (0.66, 1.25) and 0.82 (0.60, 1.12), respectively. The CL/F of alirocumab in subjects with normal liver function, mild hepatic impairment, and moderate hepatic impairment were 0.710 ± 0.298, 0.831 ± 0.270, and 0.853 ± 0.292 L/day, respectively, showing a trend toward higher CL/F of alirocumab in subjects with mild and moderate hepatic impairment in subjects with normal liver function.

Alirocumab's effect to lower serum free PCSK9 concentration and serum LDL-C tended to last shorter in subjects with mild and moderate hepatic impairment than in subjects with normal liver function. The maximum reduction rates from baseline of serum LDL-C tended to be smaller in subjects with mild and moderate hepatic impairment (33.20 ± 9.62% and 35.83 ± 14.27%, respectively) than in subjects with normal liver function (45.42 ± 7.44%).

6.2.5 Drug-drug interactions

6.2.5.1 Ezetimibe or fenofibrate (Study PKD12910, CTD 5.3.3.4-1)

A total of 3 doses of alirocumab 150 mg were subcutaneously administered Q4W in combination with ezetimibe (10 mg/day), fenofibrate (160 mg/day), or placebo to 72 non-Japanese healthy adult volunteers to evaluate the effects of ezetimibe and fenofibrate on the PK and PD of alirocumab. The GMRs of $C_{max,\,s}$ and $AUC_{0\text{-}28d}$ of alirocumab administered with ezetimibe to those of alirocumab alone (90% CI) were 0.92 (0.78, 1.09) and 0.85 (0.70, 1.03), respectively. The GMRs of $C_{max,\,s}$ and $AUC_{0\text{-}28d}$ of alirocumab administered with fenofibrate to those of alirocumab alone (90% CI) were 0.71 (0.60, 0.84) and 0.64 (0.53, 0.77), respectively.

In all treatment groups, serum LDL-C levels were lowest on Day 71. The maximum serum LDL-C reduction rate from baseline of alirocumab alone was 47.39 ± 15.59%, alirocumab + ezetimibe 56.56 ± 12.32%, and alirocumab + fenofibrate 54.34 ± 17.10%. Time to recovery to baseline serum LDL-C after the last dose of alirocumab was shorter in the alirocumab + ezetimibe and alirocumab + fenofibrate groups than in the alirocumab alone group.

6.R Outline of the review conducted by PMDA

6.R.1 Effect of the ADA on the PK of alirocumab

The applicant's explanation:

The proportions of patients who tested positive for ADA after receiving alirocumab were 2.8% (4 of 143) of subjects in the Japanese phase III study in HC patients (Study EFC13672) and 4.8% (147 of 3033) of subjects in the foreign phase III studies[1)] in HC patients. In the foreign phase III studies, the expression of a neutralizing antibody was confirmed in 1.2% (36 of 3033) of subjects. Table 20 shows the PK parameters (post hoc estimates of $C_{max, s}$ and $AUC_{0\text{-}336h}$ in a steady state calculated by the PPK analysis) of alirocumab in ADA-positive and ADA-negative subjects in each clinical study. Because alirocumab exposure at steady state in ADA-positive subjects was the same as or only slightly lower than that in ADA-negative subjects, ADA is not considered to have a significant effect on the PK of alirocumab.

Table 20. PK parameters of alirocumab in ADA-positive and -negative subjects

Study	Dose	ADA	N	$C_{max, s}$[a] (μg/mL)	$AUC_{0\text{-}336h}$[a] (μg·day/mL)
EFC13672	75 mg Q2W	Negative	134	11.2 (39)	134 (45)
		Positive	4	9.17 (22)	105 (27)
EFC11716	75 mg Q2W	Negative	33	11.1 (34)	131 (38)
		Positive	2	7.46, 10.3[b]	74.6, 116[b]
EFC12492	75 mg Q2W	Negative	156	8.71 (29)	99.2 (35)
		Positive	11	9.20 (65)	108 (77)
EFC11569	75 mg Q2W	Negative	339	7.62 (38)	85.8 (45)
		Positive	13	6.47 (41)	68.8 (48)
LTS11717	150 mg Q2W	Negative	1379	18.2 (46)	213 (53)
		Positive	58	12.0 (45)	127 (52)

Mean (CV%)
[a] Post hoc estimate as determined by a PPK analysis
[b] Individual values

PMDA's view:

The results of the Japanese and foreign phase III studies revealed no clear effect of ADA on the PK of alirocumab. However, because the foreign clinical studies also revealed the presence of a neutralizing antibody, the clinical significance of ADA expression should be determined based on data from the clinical studies, in light of the effects of ADA on the efficacy and safety of alirocumab [see Section "7.R.5.5 Production of antibodies"].

1) Studies EFC11716, EFC12492, EFC11569, LTS11717, CL-1112, EFC12732, EFC11568, CL-1110, CL-1118, and CL-1119

6.R.2 Use of alirocumab in patients with hepatic impairment

The applicant's explanation:

In the phase I study in patients with mild (Child Pugh Class A) or moderate (Child Pugh Class B) hepatic impairment (Study POP12671), the $C_{max, s}$ and AUC_{last} of alirocumab after a single subcutaneous dose of alirocumab 75 mg were similar regardless of the severity of hepatic impairment. On the other hand, the CL/F of alirocumab in subjects with mild and moderate hepatic impairment tended to be higher than that in subjects with normal liver function. In the PD assessment, alirocumab's lowering effect on serum free PCSK9 concentration and serum LDL-C levels lasted shorter in subjects with mild and moderate hepatic impairment than that in subjects with normal liver function. The mean maximum serum LDL-C reduction rates from baseline in those with mild and moderate hepatic impairment tended to be lower than in subjects with normal liver function. However, in terms of individual percentage changes from baseline serum LDL-C levels, the values were similar between subjects with mild and moderate hepatic impairment and those with normal liver function, except for 2 subjects each with mild and moderate hepatic impairment, who had lower values than others. The investigation was conducted only in 8 subjects per group. Considering these factors, the differences in the mean percentage change from baseline serum LDL-C levels between subjects with normal liver function and subjects with mild and moderate hepatic impairment could be incidental due to the dispersion of data. The patient characteristics that were considered to affect responsiveness to alirocumab (sex, age, BMI, baseline serum LDL-C levels, baseline PCSK9 concentration, and ADA expression) did not differ clearly between the 4 subjects who did not response to alirocumab well and others.

Based on these results, the differences in the effects of alirocumab on the PK and PD observed between subjects with normal liver function and those with mild or moderate hepatic impairment are considered minor and not clinically significant. Therefore, the applicant considers that dose adjustment of alirocumab is not necessary for use in patients with mild or moderate hepatic impairment.

PMDA's view:

Based on the submitted data and the applicant's explanation, dose adjustment of alirocumab is not necessary for patients with mild or moderate hepatic impairment. In terms of patients with severe hepatic impairment, there is no experience in the use of alirocumab. Further, the reason(s) for greater CL of alirocumab in patients with mild and moderate hepatic impairment than in subjects with normal liver function is not clear, and the degree of effect of severe hepatic impairment to the PK and PD of alirocumab is unknown. These facts should be highlighted in the package insert.

6.R.3 Drug-drug interactions with statins

The applicant's explanation:

The foreign phase I study in HC patients (Study CL-1001) evaluated the effect of concomitant atorvastatin on the PK of alirocumab. Alirocumab exposure was lower in the alirocumab/atorvastatin group than in the alirocumab alone group. In the PPK analysis, concomitant use of a statin was identified

as a covariate significantly affecting the PK of alirocumab, and the $AUC_{0\text{-}336h}$ of alirocumab at a steady state was estimated to be decreased by 28% to 29% when co-administered with a statin. According to an article, the administration of a statin promotes the production of PCSK9 (*Arterioscler Thromb Vasc Biol*. 2004;24:1454-1159). Given this fact, the statin may have increased serum concentration of PCSK9, the target molecule of alirocumab, and promoted the binding of PCSK9 to alirocumab, resulting in enhanced elimination of PCSK9. This mechanism may be the cause of reduced alirocumab exposure after co-administration with a statin. Baseline serum concentrations of free PCSK9 in the alirocumab/ fenofibrate and alirocumab/ezetimibe groups were higher than those in the alirocumab alone group (GMR, 1.92 and 1.24, respectively). Therefore, the reduced alirocumab exposure after co-administration with fenofibrate or ezetimibe observed in Study PKD12910 may also be attributable to the similar mechanism.

A PPK analysis estimated the $C_{max, s}$ and $AUC_{0\text{-}336h}$ (mean [CV%]) of alirocumab at steady state after multiple doses of alirocumab 75 mg subcutaneously administered Q2W with a concomitant statin to Japanese HC patients. Serum alirocumab concentration data from the Japanese phase III study (Study EFC13672) were used. The $C_{max, s}$ and $AUC_{0\text{-}336h}$ were 10.7 μg/mL (40.8%) and 3030 μg·h/mL (45.9%), respectively, in the low-dose statin group (64 subjects), and 11.6 μg/mL (37.7%) and 3320 μg·h/mL (43.3%), respectively, in the moderate- or high-dose statin group (74 subjects). Alirocumab exposure was similar regardless of the statin dose. Table 21 shows the $C_{max, s}$ and $AUC_{0\text{-}336h}$ of alirocumab at steady state in Japanese HC patients estimated by type of concomitant statin. Alirocumab exposure was similar regardless of the type of concomitant statin.

Although the combination of alirocumab with a statin reduced alirocumab exposure, there was no significant difference in the PK of alirocumab by dose or type of statin. Therefore, the applicant considers that the dose of alirocumab is not necessary to be adjusted for co-administration with various types of statins.

Table 21. PK parameters of alirocumab by type of concomitant statin

Type of concomitant statin	N	$C_{max, s}$[a] (μg/mL)	$AUC_{0\text{-}336h}$[a] (μg·day/mL)
Pravastatin	59	11.6 (40)	3330 (44)
Rosuvastatin	29	10.2 (37)	2860 (43)
Atorvastatin	21	11.7 (33)	3350 (37)
Pitavastatin	19	11.3 (50)	3220 (58)
Simvastatin	7	10.3 (31)	2890 (36)
Fluvastatin	3	10.2 (37)	2830 (41)

Mean (CV%)
[a] Post hoc estimation by the PPK analysis

PMDA's conclusion:

The applicant's explanation on no significant difference in the PK of alirocumab by dose and type of concomitant statin is justifiable. There is no need to adjust the dose of alirocumab for combination use with various types of statins.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The submitted evaluation data included the results of 1 phase I study, 1 phase II study, and 1 phase III study in Japanese patients. The following sections summarize each study.

7.1 Phase I study

7.1.1 Japanese phase I study (Study TDU12190, CTD 5.3.3.1.1, [redacted] 20[redacted] to January 2012)

A randomized, double-blind study was conducted 32 Japanese healthy adults (6 each in the alirocumab groups, 2 each in the placebo groups) at a single site in Japan. A single dose of 100, 150, 250, or 300 mg, or placebo was administered subcutaneously to evaluate the safety, tolerability, PK, and PD of alirocumab.

The study drug was administered to all 32 randomized subjects. All subjects were included in the safety analysis set. There were no discontinuations.

AEs were observed in 1 subject (fatigue) in the placebo group and 1 subject (orthostatic hypotension) in the 250 mg group. A causal relationship to the study drug was ruled out for both AEs.

No deaths, SAEs, or AEs leading to discontinuation occurred.

7.2 Phase II study

7.2.1 Japanese phase II study (Study DFI12361, CTD 5.3.5.1.1, March 2013 to January 2014)

A randomized, double-blind, placebo-controlled, parallel-group comparison study was conducted at 4 sites in Japan to evaluate the efficacy and safety of alirocumab co-administered with a statin to patients with primary HC (target sample size, 25 subjects in the placebo group and 25 subjects in each alirocumab group).

During the 12-week treatment period, alirocumab 50, 75, or 150 mg, or placebo was subcutaneously administered Q2W.

The main inclusion criteria were HC patients aged ≥20 years and ≤75 years who met the following criteria.

- Patients treated with a stable dose of atorvastatin (5-20 mg) for ≥6 weeks before screening (no atorvastatin introduction period) or during the 6-week atorvastatin introduction period after screening
- Serum LDL-C ≥100 mg/dL

- Serum TG ≤350 mg/dL

The study drug was administered to all 100 randomized subjects (25 subjects in the placebo group, 25 subjects in the 50 mg group, 25 subjects in the 75 mg group, 25 subjects in the 150 mg group), and all of them were included in the safety analysis set and the modified intent-to-treat (mITT) population. The primary efficacy analysis was performed in the mITT population. During the treatment period, 4 subjects (2, 0, 0, and 2 subjects) discontinued the treatment. The reasons for the discontinuation were AEs in 2 subjects (the 150 mg group) and poor compliance in 1 subject (the placebo group), and subject's request in 1 subject (the placebo group).

Table 22 shows the percentage changes from baseline in LDL-C (calculating method) at Week 12, which was the primary efficacy endpoint. All alirocumab groups showed significant difference as compared with the placebo group ($P < 0.0001$ for all groups; analysis of covariance using the treatment group and atorvastatin dose at screening [<10 mg, ≥10 mg] as fixed effects, and baseline LDL-C as a covariate).

Table 22. Percentage changes from baseline LDL-C (calculating method) at Week 12 (mITT)

	Placebo (N = 25)	50 mg (N = 25)	75 mg (N = 25)	150 mg (N = 25)
Baseline (mg/dL)				
Mean ± SD	121.0 ± 21.1	122.2 ± 16.6	120.9 ± 16.7	120.5 ± 16.2
Week 12 (mg/dL)				
Mean ± SD	116.0 ± 16.8	54.4 ± 16.3	46.4 ± 18.5	35.0 ± 24.1
Change from baseline at Week 12 (mg/dL)				
Mean ± SD	−5.0 ± 21.0	−67.8 ± 21.7	−74.5 ± 15.4	−85.5 ± 22.0
Percentage change form baseline at Week 12 (%)				
Mean ± SD	−2.55 ± 16.39	−54.84 ± 13.82	−62.12 ± 12.59	−71.54 ± 17.70
LMS ± SE[a]	−2.67 ± 3.09	−54.83 ± 3.09	−62.25 ± 3.09	−71.72 ± 3.09
Difference from placebo[a]				
LMS		−52.16	−59.57	−69.05
(95% CI)	–	(−60.75, −43.58)	(−68.16, −50.99)	(−77.64, −60.47)
P-value		$P < 0.0001$	$P < 0.0001$	$P < 0.0001$

If an LDC-C level at Week 12 was not available, the data was imputed by the last observation carried forward (LOCF) method.
Multiplicity adjustment: The alirocumab 150 mg group was first compared with the placebo group. If the difference was significant, the alirocumab 75 mg group was then compared with the placebo group. If the difference was significant, then the alirocumab 50 mg group was compared with the placebo group.
[a] Analysis of covariance (ANCOVA) using the treatment group and atorvastatin dose at screening (<10 mg, ≥10 mg) as fixed effects, and baseline LDL-C as a covariate

Table 23 shows the percentage changes from baseline TC, HDL-C, non-HDL-C, and TG at Week 12, the secondary efficacy endpoints.

Table 23. Percentage changes from baseline lipid parameters at Week 12 (mITT)

	Placebo (N = 25)	50 mg (N = 25)	75 mg (N = 25)	150 mg (N = 25)
TC				
Baseline (mg/dL)	203.6 ± 27.7	205.2 ± 19.9	209.2 ± 24.3	212.5 ± 22.7
Week 12 (mg/dL)	200.5 ± 20.5	139.7 ± 22.2	133.2 ± 23.3	123.7 ± 28.3
Percentage change at Week 12 (%)	−0.59 ± 11.32	−31.46 ± 11.81	−36.38 ± 7.90	−41.83 ± 11.39
HDL-C				
Baseline (mg/dL)	55.3 ± 11.2	58.8 ± 12.4	61.1 ± 15.3	68.1 ± 13.5
Week 12 (mg/dL)	56.4 ± 12.4	62.3 ± 13.5	63.9 ± 15.0	68.7 ± 12.5
Percentage change at Week 12 (%)	2.12 ± 7.99	6.42 ± 8.61	5.68 ± 12.59	1.95 ± 12.51
TG				
Baseline (mg/dL)	136.0 ± 45.2	121.3 ± 39.2	135.7 ± 64.1	119.5 ± 50.5
Week 12 (mg/dL)	140.4 ± 49.3	115.5 ± 60.6	113.8 ± 50.0	100.2 ± 28.7
Percentage change at Week 12 (%)	5.19 ± 26.62	−5.70 ± 35.29	−11.11 ± 28.02	−11.54 ± 20.13
non-HDL-C				
Baseline (mg/dL)	148.2 ± 27.0	146.4 ± 18.1	148.0 ± 23.2	144.4 ± 20.7
Week 12 (mg/dL)	144.2 ± 20.1	77.5 ± 22.0	69.3 ± 21.5	54.9 ± 23.1
Percentage change at Week 12 (%)	−1.23 ± 15.29	−46.41 ± 16.46	−53.45 ± 10.52	−62.06 ± 14.39

Mean ± SD
If values at Week 12 were not available, the data were imputed using the LOCF method.

The safety analysis revealed AEs occurring in 32.0% (8 of 25) of subjects in the placebo group, 52.0% (13 of 25) of subjects in the 50 mg group, 48.0% (12 of 25) of subjects in the 75 mg group, and 64.0% (16 of 25) of subjects in the 150 mg group. Table 24 shows AEs reported in ≥2 subjects in any treatment group.

Table 24. AEs reported in ≥2 subjects in any treatment group (safety analysis set)

	Placebo (N = 25)	50 mg (N = 25)	75 mg (N = 25)	150 mg (N = 25)
Nasopharyngitis	8.0 (2)	24.0 (6)	24.0 (6)	16.0 (4)
Injection site reaction	4.0 (1)	12.0 (3)	8.0 (2)	8.0 (2)
Cystitis	4.0 (1)	0 (0)	0 (0)	8.0 (2)
Ligament sprain	4.0 (1)	0 (0)	0 (0)	8.0 (2)
Back pain	4.0 (1)	8.0 (2)	0 (0)	4.0 (1)

% (N)

A causal relationship to the study drug could not be ruled out for AEs occurring in 4.0% (1 of 25) of subjects in the placebo group, 8.0% (2 of 25) of subjects in the 50 mg group, 8.0% (2 of 25) of subjects in the 75 mg group, and 8.0% (2 of 25) of subjects in the 150 mg group. AEs for which a causal relationship to the study drug could not be ruled out and occurred in ≥2 subjects in any treatment group were injection site reaction (1 subject in the placebo group, 1 subject in the 50 mg group, 2 subjects in the 75 mg group, and 2 subjects in the 150 mg group).

No deaths occurred. SAEs occurred in 1 subject (vertigo) in the placebo group and 1 subject (breast cancer) in the 150 mg group. A causal relationship to the study drug was ruled out for both SAEs.

AEs (breast cancer, injection site reaction) led to the discontinuation of the study drug in 2 subjects in the 150 mg group.

7.3 Phase III study

7.3.1 Japanese phase III study (Study EFC13672, CTD 5.3.5.1.5a, March 2014 to September 2015)

A randomized, double-blind, placebo-controlled, parallel-group comparison study was conducted at 31 sites in Japan to evaluate the efficacy and safety of alirocumab co-administered with a statin in HeFH patients and HC patients at high risk of cardiovascular events (target sample size, 72 subjects in the placebo group, and 144 subjects in the alirocumab group).

During the 52-week double-blind period, alirocumab 75 mg was subcutaneously administered Q2W until Week 12. Then, the dose was increased to 150 mg Q2W according to the prespecified LDL-C level at Week 8 (≥100 mg/dL in HeFH patients or non-FH patients with a history of coronary artery diseases, ≥120 mg/dL in non-FH patients with a history of or risk factors for the diseases classified as primary prophylaxis category III in the Japan Atherosclerosis Society [JAS] Guidelines). Of those who received ≥1 dose of alirocumab from Week 12, 2 subjects underwent dose increase to 150 mg.

Patients aged ≥20 years treated with a stable dose of statin for ≥4 weeks before screening were included in the study if met the following main criteria.

- Patients who meet any of the following conditions.
  - ✓ HeFH patients (A gene analysis or the clinical diagnostic criteria according to the JAS guidelines were used for diagnosis. If HeFH was strongly suspected by the investigator but the clinical diagnostic criteria were not met, a gene analysis was performed during the screening period.)
  - ✓ Non-FH patients with a history of myocardial infarction, unstable angina, coronary revascularization (percutaneous transluminal coronary angioplasty, coronary artery bypass grafting), or clinically relevant coronary artery diseases diagnosed by an invasive or non-invasive examination
  - ✓ Non-FH patients who have a history of the diseases classified as primary prophylaxis category III of the JAS Guidelines (ischemic stroke [excluding cardiogenic cerebral infarction], peripheral arterial diseases, diabetes mellitus, chronic kidney diseases) or either of the following risk factors for the above diseases:
    (1) Probability of death from coronary heart disease (CHD) over the subsequent 10 years according to NIPPON DATA80 is ≥2%.
    (2) Probability of death from CHD over the subsequent 10 years according to NIPPON DATA80 is ≥0.5% and <2%, and the patient meets at least one of the following criteria:
      (a) low HDL-cholesterolemia (serum HDL-C, <40 mg/dL)
      (b) a family history of premature coronary artery disease (first-degree relatives aged <55 years [men] or <65 years [women])

(c) abnormal glucose tolerance (fasting glucose level, <126 mg/dL; 75-g glucose tolerance at 2 hours, ≥140 mg/dL and <200 mg/dL).

- Serum LDL-C ≥100 mg/dL (HeFH patients or non-FH patients with a history of coronary artery diseases), or serum LDL-C ≥120 mg/dL (Category III patients)
- Serum TG ≤400 mg/dL

(a) Data up to the primary assessment (Week 24)

Of 216 subjects randomized (72 in the placebo group and 144 in the alirocumab group), 215 subjects (72 and 143) received the study drug, and 1 subject (the alirocumab group) was excluded due to being randomized twice by mistake. The 215 subjects were included in the safety analysis set and ITT population. The primary efficacy analysis was performed on the ITT population. A total of 10 subjects (2 and 8) discontinued by Week 24. The reasons for discontinuation were AEs in 7 subjects (1 and 6), poor compliance in 1 subject (the alirocumab group), and change of residence in 1 subject (the alirocumab group), and subject's request in 1 subject (the placebo group).

A total of 41 (14 and 27) HeFH patients were enrolled.

Table 25 shows the percentage changes from baseline LDL-C (calculating method) at Week 24, the primary efficacy endpoint. A significant difference was noted between the alirocumab and placebo groups ($P < 0.0001$, MMRM).

Table 25. Percentage changes from baseline LDL-C (calculating method) at Week 24 (ITT)

	Placebo	Alirocumab
Baseline (mg/dL)		
N	72	143
Mean ± SD	141.6 ± 26.7	141.1 ± 26.8
Week 24 (mg/dL)		
N	70	138
Mean ± SD	144.0 ± 31.3	52.8 ± 25.0
Change at Week 24 (mg/dL)		
N	70	138
Mean ± SD	2.2 ± 18.1	−88.3 ± 25.3
Percentage change at Week 24 (%)		
N	70	138
Mean ± SD	1.9 ± 14.1	−62.9 ± 15.4
LMS ± SE[a]	1.6 ± 1.8	−62.5 ± 1.3
Difference from placebo[a]		
LMS		−64.1
(95% CI)	–	(−68.5, −59.8)
P-value		$P < 0.0001$

[a] Mixed-effect model with repeated measures (MMRM) (unstructured covariance structure) using the treatment group, time point (Weeks 4, 8, 12, 16, and 24), interactions of the treatment group and time point, presence or absence of HeFH patients, and interactions of presence or absence of HeFH patients and time point as fixed effects, and baseline LDL-C and interactions of baseline LDL-C and time point as covariates.

Table 26 shows the percentage changes from baseline TC, HDL-C, non-HDL-C, and TG at Week 24, the secondary efficacy endpoints.

Table 26. Percentage changes from baseline lipid parameters at Week 24 (ITT)

	Placebo	Alirocumab
TC		
Baseline (mg/dL)	225.9 ± 34.3 (N = 72)	223.1 ± 29.9 (N = 143)
Week 24 (mg/dL)	229.9 ± 39.7 (N = 71)	134.4 ± 28.2 (N = 138)
Percentage change at Week 24 (%)	2.0 ± 11.4 (N = 71)	−39.7 ± 10.3 (N = 138)
HDL-C		
Baseline (mg/dL)	54.9 ± 15.7 (N = 72)	54.7 ± 11.8 (N = 143)
Week 24 (mg/dL)	55.1 ± 14.0 (N = 71)	59.0 ± 12.3 (N = 138)
Percentage change at Week 24 (%)	2.1 ± 12.8 (N = 71)	7.9 ± 13.8 (N = 138)
TG		
Baseline (mg/dL)	154.9 ± 112.2 (N = 72)	136.7 ± 63.5 (N = 143)
Week 24 (mg/dL)	156.7 ± 90.8 (N = 71)	112.3 ± 53.9 (N = 138)
Percentage change at Week 24 (%)	13.9 ± 47.4 (N = 71)	−12.2 ± 30.5 (N = 138)
non-HDL-C		
Baseline (mg/dL)	171.1 ± 30.4 (N = 72)	168.4 ± 29.2 (N = 143)
Week 24 (mg/dL)	174.9 ± 35.3 (N = 71)	75.3 ± 25.5 (N = 138)
Percentage change at Week 24 (%)	2.7 ± 15.1 (N = 71)	−55.3 ± 12.7 (N = 138)

Mean ± SD

AEs occurred in 62.5% (45 of 72) of subjects in the placebo group and 72.7% (104 of 143) of subjects in the alirocumab group. Table 27 shows AEs occurring in ≥3% of subjects in any treatment group.

Table 27.AEs reported in ≥3% of subjects in any treatment group (safety analysis set)

	Placebo (N = 72)	Alirocumab (N = 143)
Nasopharyngitis	16.7 (12)	26.6 (38)
Injection site reaction	2.8 (2)	10.5 (15)
Back pain	2.8 (2)	7.7 (11)
Hypertension	1.4 (1)	4.2 (6)
Dental caries	1.4 (1)	4.2 (6)
Contusion	0 (0)	4.2 (6)
Fall	0 (0)	4.2 (6)
Pharyngitis	4.2 (3)	2.1 (3)
Arthralgia	8.3 (6)	0.7 (1)
Musculoskeletal stiffness	4.2 (3)	0 (0)

% (N)

A causal relationship to the study drug could not be ruled out for AEs occurring in 5.6% (4 of 72) of subjects in the placebo group and 11.9% (17 of 143) of subjects in the alirocumab group. The AE for which a causal relationship to the study drug could not be ruled out occurring in ≥3% of subjects in any treatment group was injection site reaction (2.8% [2 of 72] subjects in the placebo group and 10.5% [15 of 143] of subjects in the alirocumab group).

No deaths occurred. SAEs occurred in 4 subjects (pyelonephritis acute, prostatitis and pancreatic carcinoma, spondylolisthesis, medical device discomfort) in the placebo group and 6 subjects (angina pectoris; vitreous haemorrhage; sudden hearing loss; pyelonephritis acute; acetabulum fracture, clavicle fracture, rib fracture, road traffic accident, and scapula fracture; acoustic neuroma) in the alirocumab group. A causal relationship to the study drug could not be ruled out for prostatitis in the placebo group.

AEs leading to the discontinuation of the study drug were reported in 2.8% (2 of 72) of subjects in the placebo group and 4.2% (6 of 143) of subjects in the alirocumab group. AEs occurring in ≥2 subjects in any treatment group were injection site reaction (0% [0 of 72] of subjects in the placebo group and 1.4% [2 of 143] of subjects in the alirocumab group).

(b) Data up to Week 52

All 205 subjects (70 subjects in the placebo group and 135 subjects in the alirocumab group) who had completed Week 24 treatment continued to receive the same study drug as one given until the primary assessment. A total of 198 subjects (66 subjects in the placebo group and 132 subjects in the alirocumab group) completed Week 52 treatment.

Table 28 shows the percentage changes from baseline LDL-C (calculating method) at Week 52.

Table 28. Percentage changes from baseline LDL-C (calculating method) at Week 52 (ITT)

	Placebo	Alirocumab
Baseline (mg/dL)		
N	72	143
Mean ± SD	141.6 ± 26.7	141.1 ± 26.8
Week 52 (mg/dL)		
N	66	133
Mean ± SD	136.1 ± 30.7	53.0 ± 25.3
Change at Week 52 (mg/dL)		
N	66	133
Mean ± SD	−5.3 ± 22.6	−88.0 ± 26.1
Percentage change at Week 52 (%)		
N	66	133
Mean ± SD	−3.2 ± 14.9	−62.7 ± 15.9
LMS ± SE[a]	−3.6 ± 1.9	−62.5 ± 1.4
Difference from placebo[a]		
LMS	–	−58.9
[95% CI]		[−63.5, −54.3]

[a] MMRM (unstructured covariance structure) using the treatment group, time point, interactions of the treatment group and time point, presence or absence of HeFH patients, and interactions of presence or absence of HeFH patients and time point as fixed effects, and baseline LDL-C and interactions of baseline LDL-C and time point as covariates

Table 29 shows the percentage changes from baseline TC, HDL-C, non-HDL-C, and TG at Week 52.

Table 29. Percentage changes from baseline lipid parameters at Week 52 (ITT)

	Placebo	Alirocumab
TC		
Baseline (mg/dL)	225.9 ± 34.3 (N = 72)	223.1 ± 29.9 (N = 143)
Week 52 (mg/dL)	217.2 ± 37.6 (N = 67)	134.1 ± 30.3 (N = 134)
Percentage change at Week 52 (%)	−3.6 ± 10.7 (N = 67)	−39.8 ± 11.0 (N = 134)
HDL-C		
Baseline (mg/dL)	54.9 ± 15.7 (N = 72)	54.7 ± 11.8 (N = 143)
Week 52 (mg/dL)	53.7 ± 13.8 (N = 67)	57.9 ± 12.3 (N = 134)
Percentage change at Week 52 (%)	−1.1 ± 12.7 (N = 67)	5.7 ± 11.3 (N = 134)
TG		
Baseline (mg/dL)	154.9 ± 112.2 (N = 72)	136.7 ± 63.5 (N = 143)
Week 52 (mg/dL)	141.4 ± 77.5 (N = 67)	118.2 ± 64.0 (N = 134)
Percentage change at Week 52 (%)	2.7 ± 31.1 (N = 67)	−8.9 ± 32.6 (N = 134)
non-HDL-C		
Baseline (mg/dL)	171.1 ± 30.4 (N = 72)	168.4 ± 29.2 (N = 143)
Week 52 (mg/dL)	163.5 ± 32.3 (N = 67)	76.3 ± 28.5 (N = 134)
Percentage change at Week 52 (%)	−3.7 ± 14.0 (N = 67)	−54.9 ± 13.7 (N = 134)

Mean ± SD

AEs occurred in 83.3% (60 of 72) of subjects in the placebo group and 90.9% (130 of 143) of subjects in the alirocumab group. Table 30 shows AEs occurring in ≥3% of subjects in any treatment group.

Table 30. AEs reported in ≥3% of subjects in any treatment group (safety analysis set)

	Placebo (N = 72)	Alirocumab (N = 143)
Nasopharyngitis	36.1 (26)	45.5 (65)
Back pain	5.6 (4)	12.6 (18)
Injection site reaction	4.2 (3)	12.6 (18)
Diabetes mellitus	5.6 (4)	8.4 (12)
Fall	6.9 (5)	7.7 (11)
Hypertension	6.9 (5)	6.3 (9)
Pharyngitis	5.6 (4)	6.3 (9)
Dental caries	1.4 (1)	6.3 (9)
Contusion	4.2 (3)	5.6 (8)
Periodontitis	1.4 (1)	4.9 (7)
Type 2 diabetes mellitus	1.4 (1)	4.9 (7)
Ligament sprain	0 (0)	4.2 (6)
Gastroenteritis	4.2 (3)	3.5 (5)
Headache	2.8 (2)	3.5 (5)
Neck pain	2.8 (2)	3.5 (5)
Diarrhoea	1.4 (1)	3.5 (5)
Dizziness	0 (0)	3.5 (5)
Spinal osteoarthritis	0 (0)	3.5 (5)
Blood creatine kinase increased	0 (0)	3.5 (5)
Arthralgia	8.3 (6)	2.8 (4)
Abdominal pain upper	5.6 (4)	2.8 (4)
Myalgia	4.2 (3)	1.4 (2)
Influenza	8.3 (6)	0.7 (1)
Seasonal allergy	6.9 (5)	0.7 (1)
Musculoskeletal stiffness	5.6 (4)	0.7 (1)
Abdominal discomfort	4.2 (3)	0.7 (1)

% (N)

A causal relationship to the study drug could not be ruled out for AEs occurring in 11.1% (8 of 72) of subjects in the placebo group and 20.3% (29 of 143) of subjects in the alirocumab group. The AE for which a causal relationship to the study drug could not be ruled out occurring in ≥3% of subjects in any treatment group was injection site reaction (4.2% [3 of 72] of subjects in the placebo group and 12.6% [18 of 143] of subjects in the alirocumab group).

No deaths occurred. SAEs occurred in 9 subjects (traumatic fracture [2 subjects]; pyelonephritis acute; prostatitis and pancreatic carcinoma; spondylolisthesis; coronary artery stenosis and myocardial infarction; medical device discomfort; intestinal obstruction; nephrotic syndrome) in the placebo group and 10 subjects (cellulitis; angina pectoris; traumatic fracture and cataract; vitreous haemorrhage; sudden hearing loss; congestive cardiomyopathy; myocardial infarction; pyelonephritis acute and muscle abscess; road traffic accident, acetabulum fracture, scapula fracture, clavicle fracture, and rib fracture; acoustic neuroma) in the alirocumab group. A causal relationship to the study drug could not be ruled out for prostatitis and nephrotic syndrome in the placebo group and congestive cardiomyopathy in the alirocumab group.

AEs leading to the discontinuation of the study drug were reported in 5.6% (4 of 72) of subjects in the placebo group and 4.9% (7 of 143) of subjects in the alirocumab group. The AE occurring in ≥2 subjects in any treatment group was injection site reaction (0% [0 of 72] of subjects in the placebo group, 2.1% [3 of 143] of subjects in the alirocumab group).

7.R Outline of the review conducted by PMDA

7.R.1 Clinical positioning

The applicant's explanation:

HC (increased LDL-C, in particular) is a major risk factor of atherosclerosis and coronary artery diseases. For the management of dyslipidemia including HC, the JAS Guidelines specify therapeutic modality and target LDL-C values according to each patient's risk. However, a guideline-recommended statin did not help reduce LDL-C to the specified target value in some patients (*Jpn J Clin Med.* 2008;66:606-610. *J Tokyo Med Assoc*. 2009;62:421-430). Because LDL-C must be certainly reduced in patients suffering HoFH, etc., an additional lipid-lowering therapy should be provided to these patients. The Japanese clinical studies were conducted in HeFH patients, non-FH patients with a history of coronary artery diseases, and Category III HC patients, who met the definitions of patients in the JAS Guidelines. The studies demonstrated the efficacy of alirocumab in those who had not achieved the target LDL-C value despite conventional standard drug therapy. Although no clinical study was conducted in HoFH patients, the Japanese and foreign phase III studies included severe HeFH patients, and foreign clinical studies included patients with homozygous, compound heterozygous, and double heterozygous FH. Because these studies demonstrated a potent LDL-C lowering effect of alirocumab in these patients, alirocumab is expected to be effective in HoFH patients as well [see Section "7.R.2 Indications and target patients of alirocumab"]. In view of these data from Japanese and foreign clinical studies, alirocumab is an option to be added to statin therapy for FH patients and non-FH patients at high risk of cardiovascular events regardless of the use of other lipid-lowering therapy.

PMDA's view:

High LDL-cholesterolemia is one of the major risk factors for arteriosclerotic diseases, and the JAS Guidelines for Diagnosis and Treatment of Dyslipidemia (2013) specifies the target LDL-C value according to the characteristics of patients. The guide also recommends strict lipid control in FH patients due to their high risk of coronary artery diseases. Currently, Japanese and foreign guidelines refer to statins as the first-line drugs for high LDL-cholesterolemia in HC patients. The Japanese phase III study (Study EFC13672) showed alirocumab's add-on LDL lowering effect and its safety that complement statin therapy. Therefore, alirocumab should be used with conventional medication including statins in patients responding inadequately to statin therapy. The details are discussed in the following Section "7.R.2 Indications and target patients of alirocumab."

7.R.2 Indications and target patients of alirocumab

The applicant's rationale:

The JAS Guidelines describe therapeutic intervention for HC as follows. For non-FH patients, whether the therapeutic intervention is required as primary or secondary prevention should be determined based on a history of coronary artery disease. For primary prevention, risks to patients are classified according to the risk factors for arteriosclerotic diseases other than coronary artery diseases, namely, a history of or concurrent diabetes mellitus, chronic kidney diseases, non-cardiogenic cerebral infarction, peripheral arterial diseases, and probability (absolute risk) of death from coronary artery diseases. A target lipid control value is determined according to the risks classified. If a non-FH patient does not achieve the target LDL-C control value despite adequate lifestyle modification, drug therapy is considered in light of the risk the patient faces. For secondary prevention, drug therapy is designed with concurrent lifestyle modification. Statins are the first-line drugs for high LDL-cholesterolemia. Patients with HeFH are at high risk of arteriosclerotic diseases. When an ischemic heart disease is suspected in a patient with HeFH, treatment of ischemic heart disease should be prioritized over exercise therapy. Statins are the first-line drugs for HeFH, and use of any one of these with other lipid-lowering drugs is recommended for strict lipid control in case of poor response to monotherapy. Since patients with HoFH are at significantly high risk of the development and progression of coronary artery diseases, potent LDL-C lowering therapy is necessary for HoFH in early life.

In the Japanese phase III study (Study EFC13672), the superiority of alirocumab co-administered with a statin to placebo was evaluated based on the primary efficacy endpoint, i.e., the percentage change from baseline LDL-C at Week 24. A subgroup analysis showed clinically significant reduction in LDL-C after the administration of alirocumab in both HeFH and non-FH patients. The results of the Japanese phase II study (Study DFI12361) and phase III study (Study EFC13672) showed that alirocumab was well tolerated in Japanese HC (HeFH and non-FH) patients.

Despite no clinical study-based evidence, alirocumab is expected to be a therapeutic option for HoFH for the following reasons: HeFH is diagnosed based on ≥2 clinical signs, namely, LDL-C ≥180 mg/dL, Achilles tendon thickening or cutaneous xanthoma, or a second-degree family history of FH or premature coronary artery diseases. Patients are diagnosed to have HoFH with TC of ≥600 mg/dL, xanthoma and an arteriosclerotic disease since childhood, and HeFH in parents (JAS Guidelines). FH is caused by dominantly inherited mutation of the genes encoding LDLR, ApoB, or PCSK9, or recessively inherited mutation of the genes encoding the LDLR adaptor protein (LDLRAP1). While FH patients generally have a heterozygous genotype, HoFH and HeFH are mostly diagnosed in clinical practice by phenotype, which does not necessarily match with genotype. The foreign phase II and III studies of alirocumab in HeFH patients (Studies EFC12492, EFC12732, CL-1003, CL-1112, CL-1119, and LTS11717) enrolled not only patients having double heterozygote of the *LDLR/ApoB* genes, double heterozygote of the *LDLR/PCSK9* genes, and compound heterozygote of the *LDLR* gene with a phenotype of HoFH, but also patients having homozygous *LDLR* genes and homozygous *LDLRAP1* genes with a genotype of HoFH. Alirocumab reduced LDL-C levels in these patients without posing safety concerns. Considering its mechanism of action, alirocumab is not expected to have efficacy in homozygous *LDLR*-null HoFH patients, in whom LDLRs are not expressed on the hepatocyte surface.

However, alirocumab can reduce LDL-C where some LDLR activity remains even in patients with a genotype of HoFH. Alirocumab, therefore, may be a therapeutic option for such patients.

The proposed package insert will be revised. The indications of alirocumab will be modified as per below, and the inclusion criteria for patients in the Japanese phase III study (Study EFC13672) will be described in the "Clinical Studies" section so that the target patients of alirocumab are more clear. Precautionary advice concerning combination use with a statin will be included in the "Precautions for Dosage and Administration" section. Furthermore, the lack of clinical experience in HoFH patients will be highlighted in the "Precautions for Indications" section.

[Applicant's draft modification] (Underlines denote addition to the proposed indications.)

Indications

Hypercholesterolemia at high risk of cardiovascular events

Familial hypercholesterolemia

However, the use of the product should be limited to:

- Patients with an inadequate response to HMG-CoA reductase inhibitors

Precautions for Indications

There is no experience in the clinical use of alirocumab for the treatment of homozygous familial hypercholesterolemia. Therefore, eligibility of the patient for alirocumab therapy should be carefully determined, and the patient should be monitored for the safety and efficacy of alirocumab during treatment (see the "1. Important Precautions" section).

Precautions for Dosage and Administration

Alirocumab should be co-administered with an HMG-CoA reductase inhibitor.

PMDA's view:

The current basic drug therapy for HC is an oral statin alone or in combination with a drug that acts by different mechanism. The efficacy and safety of alirocumab in Japanese patients were evaluated based on the results from the 2 clinical studies, the Japanese phase II study (Study DFI12361) and phase III study (Study EFC13672), conducted for the current application for approval using a concomitant statin. On the basis of these facts, alirocumab should be used in patients inadequately responding to conventional therapies including statins. Currently, treatment of dyslipidemia is import not only for improving lipid parameters but also for the actual reduction of cardiovascular events, which is the primary objective of treatment. Despite that, there are no data showing that alirocumab reduces cardiovascular events, and the safety of alirocumab in long-term use has not been demonstrated in such an extremely large patient population as in statin therapies. The use of alirocumab should be limited to patients at high risk of cardiovascular events, who are in great need of reducing LDL-C. The Japanese phase III study (Study EFC13672) conducted for the current application demonstrated significant efficacy and acceptable safety in HC patients at high risk of cardiovascular events and HeFH patients

receiving a statin, and therefore, alirocumab should target these patient population. Patients at high risk of cardiovascular events mentioned earlier should undergo risk assessment individually. Factors to consider in risk assessment (e.g., presence or absence of risk factors other than high LDL-cholesterolemia) and the fact that the Japanese phase III study (Study EFC13672) enrolled patients with HC at risk of other cardiovascular events including a history of ischemic heart disease should be communicated to healthcare professionals in an appropriate manner.

No clinical study of alirocumab was conducted in HoFH patients, and an extremely limited number of HoFH patients were enrolled in the foreign phase II and phase III studies. Thus, for this patient population, the efficacy and safety of alirocumab have not been adequately investigated. Nevertheless, HoFH is generally diagnosed based on TC values and clinical findings, and genetic testing is not common practice. The mechanism of action of alirocumab suggests its efficacy in patients who have LDLRs with a phenotype of HoFH. Therefore, alirocumab can be provided to medical institutions as a drug for not only HeFH patients but also for those with HoFH. Yet, alirocumab is not expected to show its efficacy in certain patients such as those with homozygous *LDLR*-null HoFH. Alirocumab should not be continued aimlessly if it does not exert its LDL-C lowering effect. The applicant should advise healthcare professionals to determine whether the treatment be continued based on the efficacy and safety of alirocumab in the patient. These points should be appropriately reflected in the proposed package insert. However, details of descriptions of the “Precautions for Indications” section will be finalized upon receiving comments from the Expert Discussion.

7.R.3 Efficacy of alirocumab

7.R.3.1 Rationale for the primary endpoint

Although the purpose of HC treatment is to reduce cardiovascular events, no clinical data attached to the current application demonstrating the suppressive effect of alirocumab on cardiovascular events. The Japanese phase III study (Study EFC13672), a confirmatory study in Japanese subjects, selected the percentage change in LDL-C from baseline as the primary efficacy endpoint. Therefore, PMDA requested the applicant to explain the clinical significance of the reduction in LDL-C observed after treatment with alirocumab.

The applicant’s explanation:

A number of epidemiological and pharmaceutical intervention studies showed correlations between LDL-C levels and cardiovascular events. Recent clinical researches on statins, namely, the TNT, PROVE-IT, and JUPITER studies, showed decreased LDL-C to 77 mg/dL, 62 mg/dL, and 55 mg/dL, respectively, and significant decrease in cardiovascular events as compared to the control groups (groups that demonstrated LDL-C reduced to 101 mg/dL and 95 mg/dL and a placebo group) (*N Engl J Med*. 2005;352(14):1425-1435. *N Engl J Med*. 2004;350:1495-1504. *N Engl J Med*. 2008;359(21):2195-2207). The results of the post hoc analysis of these 3 studies showed that patients who achieved LDL-C of <64 mg/dL, <40 mg/dL or 40 to 60 mg/dL, and <50 mg/dL experienced cardiovascular events less frequently than those with higher LDL-C (*Am J Cardiol*. 2007;100:747-752. *J Am Coll Cardiol*.

2005;46:1411-1416. *J Am Coll Cardiol*. 2011;57:1666-1675). A meta-analysis of 26 large-scale studies on statins for cardiovascular events was conducted in approximately 170,000 patients by the Cholesterol Treatment Trialists' Collaboration. The analysis revealed that even in patients with baseline LDL-C of <77 mg/dL, the incidences of major cardiovascular events decreased by 20% per 38.6-mg/dL reduction in LDL-C (*Lancet.* 2010;376:1670-1681). However, benefits and risks of significant reduction in LDL-C (<25 mg/dL) have not been clarified. A clinical study using ezetimibe, a non-statin drug (the IMPROVE-IT study) showed that ezetimibe used with simvastatin further reduced LDL-C than simvastatin alone, and significantly reduced the incidence of cardiovascular events during the 7-year follow-up period (simvastatin + ezetimibe, 32.7%; simvastatin alone, 34.7%) (*N Engl J Med.* 2015;372:2387-2397). These results show that LDL-C is an established effective surrogate endpoint for cardiovascular event risks. The percentage change from baseline LDL-C was thus the appropriate primary endpoint.

A relationship between reduced LDL-C and the development of major adverse cardiac events (MACE) after the administration of alirocumab was studied through analyses of the entire population and a subgroup of patients at extremely high risk of cardiovascular events, using the pooled data of 10 foreign phase III studies[2)]. In the overall population, the relationship between achieved LDL-C levels and cardiovascular outcomes tended to be linear. In the subgroup of patients at extremely high risk of cardiovascular events, the linearity of the relationship between achieved LDL-C levels and cardiovascular outcome was maintained even in lower LDL-C ranges. These results demonstrated a robust linearity between reduction in LDL-C levels and cardiovascular outcomes after the administration of alirocumab and supported the clinical significance of LDL-C lowering therapy. A clinical study (the ODYSSEY OUTCOMES study) is ongoing to evaluate the LDL-lowering effect of alirocumab on cardiovascular events.

PMDA's view:

The correlation between LDL-C and cardiovascular events has been indicated by several studies. Evidence on the cardiovascular benefits from reduced LDL-C was mostly obtained from clinical studies using statins. However, in the IMPROVE-IT study, Ezetimibe, a non-statin drug, demonstrated its suppressive effect on cardiovascular events. The foreign long-term study of alirocumab (Study LTS11717) was conducted for a comparison of changes in LDL-C from baseline between the standard therapy + alirocumab (1553 subjects) and the standard therapy (788 subjects). Subjects receiving the standard therapy + alirocumab had LDL-C decreasing from baseline to a greater degree than in those receiving the standard therapy at Weeks 24 and 78. The incidence of cardiovascular events observed up to Week 78 was 1.4% (22 of 1550) of subjects receiving the standard therapy + alirocumab and 3.0% (24 of 788) of subjects receiving the standard therapy. As explained above by the applicant, the analysis of the foreign phase III studies, though by a post hoc assessment, also suggested that a possible relationship between reduced LDL-C after the administration of alirocumab and fewer cardiovascular

2) 5 placebo-controlled studies (Studies EFC12492, CL-1112, EFC12732, EFC11568, and LTS11717) and 5 ezetimibe-controlled studies (Studies EFC11569, EFC11716, CL-1110, CL-1118, and CL-1119)

events. At present, there is no data directly demonstrating that alirocumab reduces cardiovascular events as compared with the control, but the reduction of LDL-C, regardless of whether by a statin or non-statin, is suggested to contribute to the suppression of cardiovascular events. The available long-term data shows no tendency toward increased AEs in the alirocumab group as compared with the control group. Therefore, the efficacy of alirocumab in lowering LDL-C levels has been demonstrated and thus supplying alirocumab to the clinical settings is justified at present. On the other hand, the long-term effects of alirocumab, including the duration of the LDL-C lowering effect and suppression of cardiovascular events in long term use, should be further investigated, and data on the effect of alirocumab on the incidence of cardiovascular events in actual clinical use in Japan should be collected in post-marketing surveillance, etc. The ODYSSEY OUTCOMES study is underway to investigate the ability of alirocumab to prevent recurrent cardiovascular events in patients with a history of ACS who are treated with the standard therapy for dyslipidemia. Close attention should be paid to the study results.

7.R.3.2 Efficacy in patients with HC or HeFH

The applicant's explanation about the clinical significance of alirocumab's LDL-C lowering effect in the Japanese phase III study (Study EFC13672):

In all Japanese and foreign phase III studies, the primary endpoint was the percentage change from baseline LDL-C at Week 24 in the ITT population. In the ITT analysis in the Japanese phase III study (Study EFC13672), baseline LDL-C values (mean ± SD) were 141.1 ± 26.8 mg/dL in the alirocumab group and 141.6 ± 26.7 mg/dL in the placebo group, and the LDL-C levels at Week 24 were 52.8 ± 25.0 mg/dL and 144.0 ± 31.3 mg/dL, respectively. In the alirocumab group, differences in changes in LDL-C from baseline (LMS ± SE) at Weeks 12 and 24 compared with those in the placebo group were −85.2 ± 2.7 mg/dL and −89.9 ± 3.1 mg/dL, respectively. The LDL-C levels in the alirocumab group showed a significant decrease in the same manner as that observed in the percentage changes in LDL-C. At all time points during the 24-week double-blind treatment period, many patients in the alirocumab group achieved the prespecified target LDL-C values [see Section "7.3.1 Japanese phase III study"], and the proportion of subjects who reached the target LDL-C values at Week 24 in the alirocumab group (96.7%) was higher than that in the placebo group (10.2%).

In FH patients who were unable to achieve the target LDL-C with conventional standard drug therapy and non-FH patients at high risk of cardiovascular events receiving alirocumab, the percentage changes from baseline LDL-C at Week 24 showed a statistically significant reduction in LDL-C (LMS, −64.1%) and an excellent target value achievement rate (96.7%) as compared with those receiving placebo. Since the reduction in LDL-C (mean LDL-C level at Week 24, 52.8 mg/dL; change from baseline LDL-C [LMS ± SE] at Week 24, −87.8 ± 1.8 mg/dL) was sufficient to achieve the target LDL-C set in the JAS Guidelines, the reduction in LDL-C is considered to be clinically significant.

Table 31 shows the data from the Japanese phase III study (Study EFC13672) comparing percentage changes from baseline LDL-C at Week 24 by JAS Guidelines category. Consistency between the categories was demonstrated.

Table 31. Percentage changes from baseline LDL-C at Week 24 by JAS Guidelines category (Study EFC13672, ITT)

	HeFH patients (N = 27)	Non-FH patients with a history of coronary artery disease (N = 14)	Non-FH patients in primary prevention category III (N = 102)
LDL-C value at baseline (mg/dL)[a]	150.9 ± 40.0	120.7 ± 20.4	141.3 ± 21.4
Percentage change from baseline LDL-C at Week 24 (%)[b,c]	−54.8 ± 5.0	−63.4 ± 6.2	−67.1 ± 2.7
Change from baseline LDL-C at Week24 (mg/dL)[b,c]	−82.7 ± 7.1	−80.9 ± 8.9	−93.8 ± 3.8

[a] Mean ± SD
[b] LMS ± SE
[c] MMRM using the treatment group, time point, interactions of the treatment group and time point, JAS Guidelines category, and interactions of JAS Guidelines category and time point, interactions of treatment group and time point, and interactions of treatment group, JAS Guidelines category, and time point as fixed effects, and baseline LDL-C, and interactions of baseline LDL-C and time point as covariates

PMDA's view on the efficacy of alirocumab in Japanese patients:

The Japanese phase III study (Study EFC13672) showed the superiority of alirocumab in the percentage change from baseline LDL-C at Week 24, the primary endpoint, as compared with placebo. Most patients in the alirocumab group achieved the target LDL-C specified in the JAS Guidelines at Week 24. Although data were available from only 27 HeFH patients in the alirocumab group, the LDL-C lowering effect was clear in this patient population. The LDL-C lowering effect of alirocumab was thus demonstrated in Japanese patients with HC and HeFH.

7.R.3.3 Effect on lipid parameters other than LDL-C

The applicant's explanation about the effect of alirocumab on lipid parameters other than LDL-C:

In the Japanese phase III study (Study EFC13672), changes from baseline ApoB, non-HDL-C, TC, Lp(a), TG, HDL-C, and ApoA-1 at Week 24 were investigated. Patients receiving alirocumab showed decreases in ApoB, non-HDL-C, TC, Lp(a), and fasting TG, and increases in HDL-C and ApoA-1 as compared with those receiving. Furthermore, ApoB reached the target value in the ADA/ACC Consensus Conference Report (*J Am Coll Cardiol.* 2008;51(15):1512-1524), and non-HDL-C reached the target value of the JAS Guidelines. These changes in lipid parameters were consistent with the mechanism of action and efficacy of alirocumab and caused no adverse effect on these parameters.

PMDA's view:

In the evaluation of the efficacy of alirocumab in HC patients, LDL-C lowering effect should be focused, the adverse effect of alirocumab on other lipid parameters such as HDL-C and TG also needs to be evaluated. In the Japanese phase III study (Study EFC13672), ApoB, non-HDL-C, TC, Lp(a), and fasting TG decreased and HDL-C and ApoA-1 increased in the alirocumab group. Therefore, there is no adverse effect on the safety at least for these parameters.

7.R.3.4 Long-term efficacy

The applicant's explanation:

In the Japanese phase III study in Japanese HeFH patients and non-FH patients at high risk of cardiovascular events (Study EFC13672), 91.7% (132 of 144) of subjects in the alirocumab group and 91.7% (66 of 72) of subjects in the placebo group completed the 52-week treatment. The LDL-C lowering effect of alirocumab was observed from Week 4 and lasted until Week 52, the end of the double-blind treatment period (Table 32).

Table 32. Percentage changes from baseline LDL-C at Weeks 24 and 52 (ITT)

	Week 24		Week 52	
	Placebo	Alirocumab	Placebo	Alirocumab
	N = 70	N = 138	N = 66	N = 133
Value at each time point (mg/dL) Mean ± SD	144.0 ± 31.3	52.8 ± 25.0	136.1 ± 30.7	53.0 ± 25.3
Percentage change at each time point (%)[a] LMS ± SE	1.6 ± 1.8	−62.5 ± 1.3	−3.6 ± 1.9	−62.5 ± 1.4

[a] MMRR using the treatment group, time point, interaction of the treatment group and time point, presence or absence of HeFH patients, and interaction of presence or absence of HeFH patients and time point as fixed effects, and baseline LDL-C and interaction of baseline LDL-C and time point as covariates

The secondary endpoints of changes in LDL-C, ApoB, non-HDL-C, TC, Lp(a), and fasting TG decreased, and HDL-C and ApoA-1 from baseline increased in the alirocumab group as compared to those in the placebo group at both Weeks 24 and 52.

PMDA's view:

Based on the decrease in LDL-C maintained during the long-term study, the efficacy of alirocumab is expected to last in long-term use. On the other hand, the clinical studies provided only limited data on the long-term use of alirocumab 150 mg Q2W. Alirocumab therapy in clinical settings will take longer than in the clinical studies, but no data of HoFH patients are available. Therefore, the long-term use of alirocumab should be further investigated through post-marketing surveillance, etc.

7.R.3.5 Administration of alirocumab to patients treated with LDL apheresis

PMDA requested the applicant to explain whether alirocumab can be administered to patients on LDL apheresis.

The applicant's explanation:
LDL apheresis removes LDL particles in the circulation and lowers plasma PCSK9 concentration. However, plasma LDL-C and PCSK9 concentrations begins to increase after a session of apheresis and gradually return to the pre-apheresis levels by the next session. Maintained low LDL-C achieved by LDL apheresis is explained by decreased PCSK9 concentration, the LDL-C level thus rapidly return to the pre-apheresis level without a decrease in PCSK9 concentration (*Circ Res.* 2013;113:1290-1295). Because patients who had undergone LDL apheresis within 2 months before screening or those who were scheduled to undergo LDL apheresis during the study period were excluded from the Japanese and foreign clinical studies, there are no data of this patient population. Nevertheless, there is a possibility that alirocumab's inhibitory effect on PCSK9 helps maintain LDL-C concentration achieved by LDL apheresis, leading to less frequent LDL apheresis or withdrawal from it. However, because of the suspected possibility that LDL apheresis affects the efficacy of alirocumab, alirocumab should be administered after LDL apheresis so that the concentration of alirocumab is maintained. Currently, a global study is underway outside Japan in HeFH patients requiring weekly or bi-weekly LDL apheresis (the ODYSSEY ESCAPE study). In the study, alirocumab 150 mg or placebo is administered Q2W immediately after the completion of apheresis to evaluate the effect of alirocumab on the frequency of LDL apheresis.

PMDA's view:
HC patients eligible for treatment with alirocumab may include those with FH requiring LDL apheresis. According to the applicant's explanation, alirocumab may be effective in patients undergoing LDL apheresis. Therefore, these patients can be included in the target populations of alirocumab at this point. However, because the appropriate timing of dosing of alirocumab and the efficacy and safety of alirocumab in patients undergoing LDL apheresis are not clear, the results of the ongoing ODYSSEY ESCAPE study should be promptly communicated to healthcare professionals, and appropriate measures should be taken accordingly.

7.R.4 Dosage and administration

7.R.4.1 Dosage and administration

The applicant's justification of the proposed dosage and administration:
In the Japanese phase II study (Study DFI12361) conducted in Japanese HC patients treated with a stable dose of concomitant atorvastatin, the optimal dose of alirocumab was evaluated based on percentage changes in LDL-C after the administration of alirocumab 50, 75, or 150 mg Q2W for 12 weeks. Percentage changes from baseline LDL-C at Week 12 in the alirocumab groups were compared to those in the placebo group. The differences (LMS [95% CI]) were −52.16% [−60.75, −43.58] in the alirocumab 50 mg group, −59.57% [−68.16, −50.99] in the 75 mg group, and −69.05% [−77.64, −60.47] in the 150 mg group. LDL-C decreased in an alirocumab dose-dependent manner and statistically significantly in all alirocumab groups as compared with that in the placebo group [see Section "7.2.1 Japanese phase II study"]. Furthermore, LDL-C began to decrease from Week 2, and the decreased LDL-

C were maintained at all time points during the study. Alirocumab was well tolerated within this dose range.

Because the JAS Guidelines recommend to reduce LDL-C by ≥50% from baseline in FH patients not achieving the target LDL-C of <100 mg/dL, the starting dose should be sufficient to reduce LDL-C by ≥50%. In the Japanese phase II study (Study DFI12361), LDL-C decreased by ≥50% from baseline by Week 12 in 60.0% (15 of 25) of subjects receiving alirocumab 50 mg Q2W and 80.0% (20 of 25) of subjects receiving alirocumab 75 mg Q2W. In the alirocumab groups, the upper limits of 95% confidence interval of percentage change in LDL-C were −48.69% in the 50 mg Q2W group and −56.11% in the 75 mg Q2W group; thus the 75 mg Q2W group achieved the target LDL-C of "≥50% lower from baseline." Based on these results, 75 mg Q2W was considered sufficient to achieve individual target LDL-C in many patients. Therefore, the Japanese phase III study (Study EFC13672) used the starting dosage of 75 mg Q2W.

The Japanese phase II study (Study DFI12361) showed decreases in LDL-C in an alirocumab dose-dependent manner. The difference in percentage changes from baseline LDL-C at Week 12 as compared with placebo was larger in the alirocumab 150 mg Q2W group than in the 75 mg Q2W group. Alirocumab was maximally effective at 150 mg Q2W. The target patients in the phase III study (Study EFC13672) and patients expected to be treated with alirocumab in clinical settings (HeFH patients and non-FH patients at high risk of cardiovascular events) were considered to have a higher risk of cardiovascular events than those evaluated in the Japanese phase II study (Study DFI12361). In the Japanese phase II study (Study DFI12361), alirocumab 150 mg Q2W was well tolerated and reduced LDL-C more substantially than 75 mg Q2W. Therefore, a dose increase to 150 mg Q2W was expected to further reduce LDL-C of patients at high risk of cardiovascular events who did not achieve the target LDL-C value with alirocumab 75 mg Q2W. The Japanese phase III study in Japanese patients (Study EFC13672) thus employed a dosing regimen with the starting dose of 75 mg of alirocumab Q2W and the optional dose increase to 150 mg Q2W for patients not responding to 75 mg Q2W well and failing to achieve the target LDL-C.

The dose interval was determined based on the following results of 2 dose-finding studies in non-Japanese subjects (Studies DFI11565 and CL-1003). In these 2 studies, a certain level of LDL-C lowering effect of alirocumab Q2W lasted during the 2-week dose intervals regardless of the base treatment and dose patients were receiving, even at the lowest dose examined (50 mg Q2W). The reduction of LDL-C from baseline was significant at Week 12 after the dose of alirocumab Q4W. In patients treated with a stable dose of statin, the effect was not maintained over the 4-week dosing interval. Therefore, Q2W was selected as an appropriate frequency for the evaluation in the phase II study (Study DFI12361), which was a Japanese dose-finding study.

The Japanese phase III study (Study EFC13672) was conducted to investigate the efficacy of alirocumab used in combination with a stable dose of statin in HeFH patients and non-FH patients at high risk of

cardiovascular events. In the alirocumab group, treatment was started at 75 mg Q2W, and the dose was increased to 150 mg Q2W from Week 12 if the LDL-C at Week 8 did not reach the prespecified target value. The percentage changes from baseline LDL-C at Week 24 significantly decreased in the alirocumab (75 mg Q2W/150 mg Q2W) group as compared to those in the placebo group (differences in percentage changes from baseline LDL-C as compared with those in the placebo group [LMS], −64.1%). The efficacy of alirocumab was noted from Week 4 and maintained until Week 24, the primary assessment point. Most subjects (138 of 140 subjects) achieved their prespecified target LDL-C values with alirocumab 75 mg Q2W and maintained the values after Week 12 without dose increase. The 2 subjects who did not achieve their target LDL-C values with alirocumab 75 mg Q2W underwent dose increase to 150 mg Q2W at Week 12 under blinded conditions. The effect of dose increase was confirmed in both subjects. The degree of reduction in LDL-C after the dose increase was equivalent to the difference in percentage change in LDL-C (approximately 9%) between the 75 mg Q2W and 150 mg Q2W groups in the Japanese phase II study (Study DFI12361). The results of the Japanese phase III study (Study EFC13672) showed that alirocumab 75 mg and 150 mg Q2W were well tolerated in Japanese patients, and the safety profile of alirocumab was similar regardless of dose increase. Furthermore, the Japanese phase II study (Study DFI12361) showed that alirocumab 75 mg Q2W and 150 mg Q2W were both well tolerated without clear difference. Accordingly, treatment with alirocumab should be started at 75 mg Q2W, because the therapeutic target LDL-C was achieved and maintained during the treatment period by the dose, and the dose should be increased to 150 mg Q2W for patients with difficulty in achieving the therapeutic target LDL-C by 75 mg Q2W.

Only 2 of 140 subjects failed to achieve the prespecified target LDL-C at Week 8, needing to increase the dose to 150 mg Q2W in the Japanese phase III study (Study EFC13672). PMDA therefore requested the applicant to explain the rationale for having the 150 mg Q2W regimen in Japan.

The applicant's explanation:
In the Japanese phase III study (Study EFC13672), the dose increase criteria were defined according to LDL-C levels (≥100 mg/dL in HeFH patients or non-FH patients with a history of coronary artery disease, ≥120 mg/dL in non-FH patients in primary prevention category III) as per the JAS Guidelines. For subjects meeting these criteria at Week 8, blinded dose increase was compulsory. Table 33 shows the LDL-C levels of the 2 subjects experienced dose increase. The LDL-C further decreased by 6.2% in Subject 1 and 9.2% in Subject 2.

Table 33. LDL-C levels in patients with and without dose increase (mg/dL)

	Without dose increase[a] (N = 138)	With dose increase (N = 1)	With dose increase (N = 2)
Baseline	140.0 ± 24.4	227	240
Week 8	49.1 ± 21.4	104	168
Week 12	49.3 ± 20.7	104	169
Week 24	51.9 ± 23.6	90	147

[a], Mean ± SD

In 6 foreign phase III studies[3)] that used a statin as a basic therapy, alirocumab was started at 75 mg Q2W, and the dose was increased to 150 mg Q2W at Week 12 if the LDL-C level at Week 8 did not meet the criteria prespecified for each subject according to their baseline cardiovascular events risk. The criteria for dose increase were specified as LDL-C ≥70 mg/dL for patients at extremely high risk of cardiovascular events and LDL-C ≥100 mg/dL for patients at high risk of cardiovascular events. These criteria basically follow the US and EU guidelines (National Cholesterol Education Program [NCEP] Adult Treatment Panel III [ATP III] Guidelines Update 2004; European Society of Cardiology and European Atherosclerosis Society [ESC/EAS] Guidelines Updates 2011 and 2012). Of the 6 studies, 2 (Studies EFC12492 and CL-1112) were conducted in FH patients only, and had a high proportion of subjects experiencing dose increase (38.6%-43.4% in patients who received ≥1 dose from Week 12). These studies also revealed high mean baseline LDL-C. In other studies, 14.0% to 18.5% of subjects who received ≥1 dose from Week 12 onward experienced dose increase. A pooled analysis of the 6 studies showed that the percentage change in LDL-C from Week 12 until Week 24 (mean ± SD) was −14.2 ± 30.5% in patients experiencing dose increase, showing further improvement after dose increase. The proportion of subjects whose LDL-C decreased by ≥10% from Week 12 until Week 24 was 58.4% (178 of 1291 subjects).

Tables 34 and 35 show the evaluation results on the incidence of AEs by dose increase at Week 12 based on the pooled analysis of 8 foreign phase III studies.[4)] No clear difference was noted in the profile of AEs due to dose increase.

Table 34. Incidence of AEs by dose increase in pooled data from placebo-controlled studies

	With dose increase (N = 228)	Without dose increase (N = 432)
Back pain	3.9 (9)	1.9 (8)
Sinusitis	3.5 (8)	2.8 (12)
Gastroenteritis	3.1 (7)	1.9 (8)
Diarrhoea	3.1 (7)	1.2 (5)
Abdominal pain	3.1 (7)	0.5 (2)
Muscle spasms	2.2 (5)	1.6 (7)
Oedema peripheral	2.6 (6)	0.7 (3)
Influenza like illness	2.2 (5)	1.4 (6)
Creatine kinase increased	2.2 (5)	0.9 (4)

% (N)
AEs with an incidence of ≥2.0% and ≥0.5% higher in the dose-increase group than in the non-dose-increase group

3) Studies EFC12492, CL-1112, EFC11568, EFC11569, CL-1110, and CL-1118
4) 3 placebo-controlled studies (Studies EFC12492, CL-1112, and EFC11568) and 5 ezetimibe-controlled studies (Studies EFC11569, EFC11716, CL-1110, CL-1118, and CL-1119)

Table 35. Incidence of AEs by dose increase in pooled data from ezetimibe-controlled studies

	With dose increase (N = 180)	Without dose increase (N = 606)
Hypertension	5.0 (9)	2.0 (12)
Accidental overdose	3.9 (7)	3.3 (20)
Myalgia	3.9 (7)	3.0 (18)
Headache	3.9 (7)	1.3 (8)
Sinusitis	2.2 (4)	1.3 (8)
Bronchitis	2.2 (4)	0.8 (5)

% (N)
AEs with an incidence of ≥2.0% and ≥0.5% higher in the dose-increase group than in the non-dose-increase group

In the pooled data from 6 foreign phase III studies[3)] that used a statin as a background therapy, predictive factors for dose increase were investigated. The difference between baseline LDL-C and the target LDL-C was considered the most important predictive factor for dose increase. Dose increase was required in 9.0% (43 of 478) of subjects with the difference between baseline LDL-C and the target LDL-C of <30 mg/dL, 19.6% (78 of 398) of subjects with the difference of ≥30 mg/dL and <60 mg/dL, 42.8% (98 of 229) of subjects with the difference of ≥60 mg/dL and <90 mg/dL, and 65.1% (121 of 186) of subjects with the difference of ≥90 mg/dL. This predictive factor was considered applicable to Japanese patients. Both 2 Japanese subjects who underwent dose increase had HeFH. The baseline LDL-C of each subject was 227 and 240 mg/dL, and the difference from the target LDL-C was ≥90 mg/dL. Based on these results, it is appropriate to include alirocumab 150 mg Q2W in the dosage and administration for use in Japan and that alirocumab 150 mg Q2W can meet a medical need in Japanese HC patients whose LDL-C levels remain high even with statin therapy.

PMDA's view:
The Japanese phase III study (Study EFC13672) demonstrated a statistically significant difference in percentage changes from baseline LDL-C at Week 24 between the alirocumab group and the placebo group. The achievement rate for the target LDL-C and other results also indicated the clinically significant efficacy of alirocumab. These results demonstrate the acceptable safety of alirocumab. Meanwhile, other than the 2 subjects experiencing dose increase to 150 mg Q2W according to the dose increase criteria met at Week 8, the majority of subjects (138) remained at the starting dose of 75 mg Q2W, and therefore 75 mg Q2W should be the standard dosing regimen of alirocumab for the treatment of HC and HeFH.

In the Japanese clinical studies, the dosing regimen of 150 mg Q2W was used for 25 subjects in the Japanese phase II study (Study DFI12361) and 2 subjects in the Japanese phase III study (Study EFC13672) only. Therefore, investigation was inadequate on the efficacy and safety of alirocumab 150 mg Q2W and the effect of dose increase from 75 mg Q2W to 150 mg Q2W in Japanese subjects. The LDL-C level for the dose increase criteria differs between the foreign clinical studies and the Japanese clinical studies. The foreign studies were designed to allow dose increase when the LDL-C level was ≥70 mg/dL. Subjects at extremely high risk of cardiovascular events, in particular, would undergo dose

increase even if alirocumab had reduced LDL-C to a level which did not require dose increase in the Japanese clinical studies. Therefore, it should be noted that, in the foreign studies, there were subjects experiencing dose increase when their LDL-C was lower than the level requiring dose increase in the Japanese clinical studies. In the clinical use of alirocumab in Japan, the proportion of patients requiring dose increase is expected to be lower than the proportion of patients experiencing dose increase in the foreign clinical studies (approximately 40% in the studies conducted in FH patients only, and approximately 15% in other studies). In fact, only 2 of 140 subjects in the Japanese clinical study underwent dose increase, which suggests a low proportion of Japanese patients required dose increase. Data of Japanese subjects experiencing dose increase are available from only the 2 subjects in the Japanese phase III study (Study EFC13672), precluding adequate investigation. The Japanese phase II study (Study DFI12361), however, demonstrated greater LDL-C lowering effect at 150 mg Q2W than 75 mg Q2W without particular safety concerns posed in subjects in the 150 mg Q2W group. The foreign clinical studies demonstrated an additional LDL-C lowering effect of alirocumab increased from 75 mg Q2W to 150 mg Q2W. AE profiles of subjects who experienced dose increase were compared with those of subjects who did not. The results showed no dose increase-related AEs nor any AEs which tended to increase significantly following dose increase. The foreign clinical data suggested that patients (including those with FH) having greater gap between the baseline and target LDL-C were more likely to require dose increase. Therefore, in clinical settings in Japan, when alirocumab is administered to patients with higher LDL-C including those with HeFH, who were rare in Japanese clinical studies, dose increase to a high dose may be necessary to achieve the target LDL-C. Taking these points into consideration, dose increase of alirocumab from 75 mg Q2W to 150 mg Q2W will offer a great benefit as a therapeutic option to clinical settings in Japan. Still, because of limited clinical experience with alirocumab 150 mg Q2W in Japanese patients and unknown long-term efficacy and safety of the high dose, post-marketing data collection is essential.

7.R.4.2 Type and dose of a concomitant statin

PMDA requested the applicant to explain whether alirocumab is effective and safe regardless of the type and dose of concomitant statin.

The applicant's explanation:

A statin promotes the production of PCSK9, the target molecule of alirocumab, and is partially involved in PCSK9-mediated clearance. The effect of statin dose levels on LDL-C percentage changes was evaluated. The Japanese phase III study (Study EFC13672) was conducted in patients who failed to achieve the target LDL-C despite receiving a stable dose of statin for ≥4 weeks. A total of 6 statins (pravastatin, simvastatin, fluvastatin, atorvastatin, pitavastatin, and rosuvastatin) were accepted for use in the study without specific doses. The actual doses of concomitant statin administered to the subjects of the study ranged widely from the minimum specified dose to a high dose used for statin intensive therapy. Table 36 shows the results of evaluation of statin at higher or low-doses categorized based on the usual starting dose according to the distribution of subjects for each statin. Based on the LDL-C percentage changes from baseline at Week 24 in the ITT of the Japanese phase III study (Study

EFC13672), no specific type or dose level of stain was considered likely to affect the efficacy of alirocumab, despite difficulty in conclusive discussion due to the limited number of subjects in each category.

Table 36. LDL-C Percentage changes from baseline at Week 24 by statin type (ITT) (Study EFC13672)

Statin	Dose	N	Mean LDL-C percentage change [95% CI]
All concomitant statins	–	208	−64.8 [−69.1, −60.5]
Pravastatin	Low dose	52	−65.2 [−73.2, −57.2]
	High dose	43	−68.5 [−76.8, −60.2]
Simvastatin	Low dose	7	−44.6 [−79.2, −10.0]
	High dose	1	–
Fluvastatin	Low dose	1	–
	High dose	3	−63.4 [−107.0, −19.8]
Atorvastatin	Low dose	24	−67.4 [−87.3, −47.5]
	High dose	9	−67.5 [−78.8, −56.2]
Pitavastatin	Low dose	15	−58.0 [−75.2, −40.8]
	High dose	14	−63.4 [−77.0, −49.8]
Rosuvastatin	Low dose	14	−72.5 [−92.5, −52.4]
	High dose	25	−49.8 [−64.8, −34.8]

For the foreign phase III studies,[5)] subgroup analyses were performed on intensive statin therapy (atorvastatin 40 mg or 80 mg, rosuvastatin 20 mg or 40 mg), non-intensive statin therapy (simvastatin [any dose], atorvastatin <40 mg, rosuvastatin <20 mg), and by statin dose level at randomization. No interaction between alirocumab and statin dose levels was observed in the subgroups of any studies.

Incidences of AEs were evaluated in the safety analysis set of the Japanese phase III study (Study EFC13672) by statin type at high or low dose. Although the small sample size of each subgroup precluded an accurate interpretation, the AE profiles of the subgroups were generally similar.

Table 37 shows the results of investigation on AEs reported from the 12 Japanese and foreign phase II studies and foreign phase III studies using concomitant statins.[6)] In a pooled analysis of the placebo-controlled studies, the incidence of diabetes mellitus was slightly higher in the high-dose atorvastatin subgroup of the alirocumab groups than in the low-dose atorvastatin subgroup. The trend in the placebo group was similar. In other analyses, the AE profiles were similar regardless of statin type and statin dose level, as in the Japanese phase III study (Study EFC13672). These results revealed no trends indicative of safety concerns with alirocumab 75 mg Q2W or 150 mg Q2W, regardless of the type and dose level of concomitant statin.

5) Studies EFC12492, CL-1112, EFC11568, EFC11569, EFC12732, CL-1110, CL-1118, and LTS11717
6) 9 placebo-controlled studies (Studies EFC12492, CL-1112, EFC12732, EFC11568, LTS11717, DFI11565, DFI11566, CL-1003, and DFI12361) and 3 ezetimibe-controlled studies (Studies EFC11569, CL-1110, and CL-1118)

Based on the above results, alirocumab is expected to be effective and safe regardless of the type and dose of concomitant statin.

Table 37. Incidence of AEs by type and dose of statin (pooled analysis of Japanese and foreign phase II studies and foreign phase III studies)

		Atorvastatin		Rosuvastatin		Simvastatin	
		Low-dose	High-dose	Low-dose	High-dose	Low-dose	High-dose
Pooled placebo-controlled studies	Placebo	67.5 (104/154)	77.7 (254/327)	79.7 (47/59)	75.0 (246/328)	81.5 (22/27)	80.6 (283/351)
	Alirocumab	70.0 (215/307)	76.0 (508/668)	77.6 (90/116)	74.8 (464/620)	84.3 (43/51)	79.8 (521/653)
Poooled ezetimibe-controlled studies	Ezetimibe	69.2 (18/26)	63.5 (66/104)	50.0 (8/16)	67.2 (41/61)	75.0 (3/4)	84.4 (38/45)
	Alirocumab	59.4 (19/32)	70.0 (145/207)	64.0 (16/25)	70.9 (83/117)	80.0 (4/5)	79.0 (79/100)

% (N)

PMDA's view:

The Japanese phase III study (Study EFC13672) demonstrated the efficacy and safety of alirocumab co-administered with a statin. As described earlier, alirocumab should be administered as an add-on drug to patients who do not respond adequately to statin therapy [see Sections "7.R.1 Clinical positioning" and "7.R.2 Indications and target patients of alirocumab"]. The efficacy and safety of alirocumab were analyzed by type and dose level of statin used in the Japanese and foreign clinical studies. Although varied subgroup sizes and other factors precluded accurate interpretation of the analyses results, the efficacy and safety of alirocumab were demonstrated to some degree regardless of the type and dose level of concomitant statin. Therefore, alirocumab is expected to have a clinically significant LDL-C lowering effect and acceptable safety regardless of the type and dose level of a statin to be used with alirocumab in clinical settings.

In light of the descriptions in Sections 7.R.4.1 and 7.R.4.2, dosage and administration should be described as follows. However, the descriptions will be finalized based on comments from the Expert Discussion.

Dosage and Administration (PMDA's proposal)

The usual adult dosage is 75 mg of alirocumab (genetical recombination) administered by subcutaneous injection once every 2 weeks. The dose may be increased to 150 mg for patients not adequately responding to 75 mg.

Precautions for Dosage and Administration

Alirocumab should be co-administered with an HMG-CoA reductase inhibitor. (The efficacy and safety of alirocumab monotherapy have not been established in Japanese patients.)

7.R.5 Safety

7.R.5.1 Excessive decrease in LDL-C

PMDA requested the applicant to summarize available knowledge on the risks associated with low LDL-C or cholesterol regardless of the use of alirocumab, and to explain whether it was possible to infer that such risks would not pose an obstacle to the use of alirocumab.

The applicant's explanation:

The mechanism of action of alirocumab is characterized by accelerated increase in LDL-C removal capacity and enhanced cell transport. Cholesterol is an essential component of the cell membrane and is a precursor for the synthesis of steroid hormone, vitamin D, and bile acid. A long standing dispute on adverse effects related to idiopathic low cholesterol and decreased LDL-C revealed that most of potentially harmful events are categorized into cancer, neurological events (nerve disorders, neurocognitive events, and hemorrhagic stroke) and diabetes mellitus. During the IMPROVE-IT study, the median LDL-C levels were lower in the simvastatin/ezetimibe group (53.7 mg/dL) than in the simvastatin alone group (69.5 mg/dL). On the other hand, the results of the 7-year follow-up showed no difference between the groups in the safety endpoints including the incidence of cancer and death from cancer (*N Engl J Med.* 2015;372:2387-2397). While these observations have indicated potential safety concerns related to cancer, neurological events, diabetes mellitus, and steroid hormone, few point out safety concerns regarding extremely low LDL-C at present.

Safety with markedly low LDL-C in the Japanese clinical studies: Table 38 shows the incidences of AEs in patients with LDL-C levels of <25 mg/dL at 2 consecutive measurement points in the Japanese clinical studies. In the Japanese phase II study (Study DFI12361), the incidences of AEs in these patients were similar to that in each dose group irrespective of LDL-C levels. No SAE or AE led to the discontinuation of the study drug, and no specific safety concern was noted in patients with LDL-C levels of <25 mg/dL at 2 consecutive measurement points. In the Japanese phase III study (Study EFC13672), the incidences of AEs in patients whose LDL-C levels decreased to <25 mg/dL at 2 consecutive measurement points did not differ significantly as compared to other subgroups. In the placebo groups of the Japanese clinical studies, no patients had LDL-C levels of <25 mg/dL at 2 consecutive measurement points.

Table 38. Incidences of AEs in patients with LDL-C levels of <25 mg/dL at 2 consecutive measurement points (Japanese clinical studies)

	Study DFI12361			Study EFC13672
	Alirocumab 50 mg	Alirocumab 75 mg	Alirocumab 150 mg	Alirocumab
Proportion of patients concerned (%)[a]	8.0 (n = 2/25)	16.0 (n = 4/25)	37.5 (n = 9/25)	12.1 (n = 17/140)
Incidence of AEs (%)[b]	50.0 (n = 1/2)	50.0 (n = 2/4)	55.6 (n = 5/9)	82.4 (n = 14/17)

[a] (Number of patients with LDL-C levels of <25 mg/dL at 2 consecutive measurement points)/(Overall patients)

[b] (Number of patients with LDL-C levels of <25 mg/dL at 2 consecutive measurement points who experienced an AE)/(Number of patients with LDL-C levels of <25 mg/dL at 2 consecutive measurement points)

In the Japanese phase III study (Study EFC13672), the incidence of diabetes mellitus in subjects whose LDL-C decreased to <25 mg/dL at 2 consecutive measurement points (17.6%, 3 of 17 subjects) was higher than in other subjects (5.6%, 7 of 126 subjects). However, because of the small number of patients with low LDL-C and the exploratory nature of the analysis, this result is specific, and no specific safety concerns were identified. Of the 17 subjects with decreased LDL-C to <25 mg/dL at 2 consecutive measurement points, 3 subjects (2.1%) in the alirocumab group had LDL-C levels of <15 mg/dL at 2 consecutive measurement points, but no alirocumab-related AE was observed.

Safety with continuous and marked decrease in LDL-C: In the foreign clinical studies, the evaluation of potential safety concerns associated with low LDL-C (cancer, neurological events, endocrine effects [syntheses of gonadal and adrenocortical hormones], vitamin E deficiency, and hemolytic anemia) revealed no signs of neurological and neurocognitive events. Patients with a history of hemorrhagic stroke, one of neurological events were excluded from the foreign phase III studies, and in these studies, no event was identified as confirmed de novo hemorrhagic stroke in patients with LDL-C levels of <25 mg/dL. Generally, the incidence of neoplasm was low and similar between the alirocumab group and the placebo group. No data suggested a relationship between alirocumab exposure and the development of neoplasm. Of patients receiving treatment for ≥52 weeks, those with LDL-C levels of <25 mg/dL experienced malignant tumor-related AEs (6 of 216 subjects), namely, basal cell carcinoma (2 events), squamous cell carcinoma (2 events), Bowen's disease, laryngeal cancer, squamous cell carcinoma of skin, and squamous cell carcinoma of the oral cavity (1 event each). The results showed that increased proportion of patients with their vitamin E decreased below the lower limit of normal is observed when their LDL-C level remain <25 mg/dL (hazard ratio, 5.23 [95% CI, 1.77; 15.47]). However, no neurocognitive AEs or neurological disorder-related AEs were reported in patients with their vitamin E levels below the lower limit of normal (31 subjects in the alirocumab group, 1 subject in the placebo group) [see Sections "7.R.5.7 Effect on eyes" and "7.R.5.8 Effect on hormones" for ophthalmologic events and steroid hormone].

As stated above, in the analyses of whole AE data and specific safety data requiring special attention, such as on neurological events, neurocognitive events, vitamin E levels, and steroid hormone, the safety in patients with LDL-C levels of <25 mg/dL or <15 mg/dL at 2 consecutive measurement points was compared with other patients. The results did not raise safety concerns associated with low LDL-C in these patients.

Alirocumab 75 mg Q2W, the starting dose in the current application, caused low-LDL-C only in a limited number of patients. The dose is to be increased to 150 mg Q2W when LDL-C need to be further reduced to achieve the target. Given this situation, alirocumab is able to reduce the number of patients suffering significantly low LDL-C in clinical settings.

PMDA requested the applicant to explain whether the discontinuation of alirocumab should be considered when LDL-C decreases to below a certain level during treatment.

The applicant's explanation:

There are no data suggesting safety concerns about decreased LDL-C to <25 mg/dL. The clinical studies including the PROVE-IT study provided evidence of potential benefits of decreased LDL-C (*N Engl J Med*. 2004;350:1495-1504). Based on such clinical evidence currently available, the discontinuation of alirocumab should not be recommended. The benefit-risk balance in patients with continuous LDL-C of <25 mg/dL are not clear. Nevertheless, simply discontinuing alirocumab will result in the rebound of LDL-C level to baseline and may increase the risk of cardiovascular events. Instead of discontinuing alirocumab, physicians should assess the entire lipid-lowering therapy given to the patient before determining whether the therapy should be modified.

PMDA's view:

Some subjects treated with alirocumab in the clinical studies had serum LDL-C of as low as <25 mg/dL. Such markedly low LDL-C had never been achieved with conventional HC therapy, and the effect of such low LDL-C has not been clear enough. Data on safety particularly in the long-term treatment with alirocumab are insufficient. On the other hand, the currently available clinical studies data suggest that a marked reduction in LDL-C did not influence the occurrence of AEs. A number of discussions on risks associated with low LDL-C, including the carcinogenicity and cerebral hemorrhage, regardless of whether due to alirocumab, have not identified events that confirm such risks. Consequently, there is no basis for strong concerns about increasing low LDL-C-associated risks at present. Given these observations, although alirocumab can be increased from the starting dose of 75 mg Q2W to 150 mg for patients failing to achieve the target LDL-C with the starting dose, excessive reduction of LDL-C levels should preferably be avoided. At the same time, each clinical setting may face a decision on a comprehensive review of their lipid control policy, including the discontinuation of alirocumab and selection of a concomitant drug, depending on the patient's condition. Despite that, it is not necessary at this point to consider specific measures, such as defining across-the-board criteria for discontinuation, to prevent a decrease in post-alirocumab LDL-C to below a specific threshold. Because cholesterol also plays an important role in the living body, data on the effect of markedly low LDL-C should be further collected, a relationship between LDL-C levels and safety should be continuously evaluated in post-marketing surveillance, etc., and appropriate measures should be taken as necessary when new knowledge is made available.

7.R.5.2 Injection site reaction

Because the drug product is meant for a subcutaneous injection, PMDA requested the applicant to explain AEs related to the injection site.

The applicant's explanation:

In the Japanese phase III study (Study EFC13672), local injection site reactions (symptoms related to local injection site reactions [pain, redness, and pruritus] reported by investigators) were reported in 12.6% (18 of 143) of subjects in the alirocumab group and 4.2% (3 of 72) of subjects in the placebo

group. All events were mild. None of the 2 subjects experiencing dose increase to 150 mg Q2W had injection site reaction. In the alirocumab group, local injection site reactions occurred in 20.9% (14 of 67) of subjects with a history of allergy, and the incidence was higher than in subjects with no history of allergy (5.3%, 4 of 76). The incidence in female subjects (16.7%, 10 of 60) was higher than in male subjects (9.6%, 8 of 83), and the incidence in subjects aged ≥65 years (20.0%, 10 of 50) was higher than in subjects aged <65 years (8.6%, 8 of 93).

According to the pooled global safety data,[7)] the incidence of local injection site reactions (symptoms related to local injection site reactions [pain, redness, and pruritus] reported by the investigators or those classified into the HLT "injection site reaction") was 6.1% (205 of 3340) of subjects in the alirocumab group and 4.1% (78 of 1894) of subjects in the pooled control group. Although these AEs occurred more frequently in the alirocumab group than in the pooled control group, they were mostly mild and transient. A SAE (injection site reaction) was observed in 1 subject in the alirocumab group. This isolated event occurred at 393 days postdose and resolved without treatment. Injection site reactions were reported throughout the treatment period, with no dose-dependent relationship in the increase in events between 75 mg Q2W and 150 mg Q2W or no specific tendencies in the incidence by injection route (abdomen, upper arm, and thigh). Based on these results and the available study data, due to the possibility that local injection site reactions occur as adverse reactions of alirocumab, "injection site reaction" was included in the "Other Adverse Reactions" section of the proposed package insert.

Injection site reactions to the administration of alirocumab were generally mild and transient, and were mostly resolved without treatment during the continued treatment. In the Japanese and foreign clinical studies, injection site reactions were treated with oral or topical antihistamines and topical corticosteroids, as with injection site reactions caused by general injection or vaccination. Therefore, local injection site reactions caused by alirocumab can also be treated locally and conservatively with cold compress, corticosteroids, antihistamines, etc. as per the orthodox treatment for adverse reactions to inoculation. Repeated injection to the same site should be avoided to prevent the development and aggravation of injection site reactions.

PMDA's view:
In the clinical studies, injection site reactions-related AEs were reported more frequently in the alirocumab group than the placebo group, and were observed regardless of the dose level and duration of treatment. Therefore, attention should be paid to the occurrence of injection site reactions during treatment with alirocumab. The severity of AEs and the small number of discontinued patients suggest no clinically significant concerns over injection site reactions. Yet, precautionary advice on the reduction of injection site reaction-related AEs, including changing the injection site at every injection, should be given.

7) Pooled data from 9 placebo-controlled studies (Studies DFI12361, DFI11565, DFI11566, CL-1003, EFC11568, EFC12492, CL-1112, EFC12732, and LTS11717) and 5 ezetimibe-controlled studies (Studies EFC11569, CL-1110, CL-1118, EFC11716, and CL-1119)

7.R.5.3 Allergic events

The applicant's explanation about allergic events during treatment with alirocumab:

AEs related to systemic allergy were summarized based on preferred terms (PTs) categorized into Standardised MedDRA Queries (SMQ) of "hypersensitivity" except those related to local injection site reactions. In the Japanese phase II study (Study DFI12361), AEs related to systemic allergy (conjunctivitis, allergic bronchitis, stomatitis, dermatitis, rash) were reported in 6 subjects in the alirocumab group and none in the placebo group. A causal relationship to the study drug was ruled out for all of these events. No SAE or AE led to the discontinuation of the study drug. Although 1 subject who experienced allergic bronchitis had a history of allergic bronchitis and tested positive for ADA with neutralizing antibody, a causal relationship between allergic bronchitis and the study drug was ruled out. In the Japanese phase III study (Study EFC13672), the incidence of AEs related to systemic allergy was lower in the alirocumab group (7.7%, 11 of 143 subjects) than in the placebo group (18.1%, 13 of 72 subjects), and no SAE or AE related to systemic allergy led to the discontinuation of the study drug in any treatment group. One ADA-positive subject in the alirocumab group experienced dermatitis contact (non-allergic dermatitis contact of right wrist). This event occurred approximately 2 months after the last dose of the study drug and a causal relationship to the study drug was ruled out.

Table 39 shows the incidences of systemic allergy related-AEs (all AEs combined and AEs that occurred more frequently in the alirocumab group than in the placebo group [AEs reported in ≥0.3% of subjects in the alirocumab group]) based on the pooled results from the placebo-controlled studies in the pooled global safety data.[7)] Systemic-allergy related SAEs were reported in 0.4% of subjects in each treatment group (9 of 2476 in the alirocumab group and 5 of 1276 in the placebo group). A causal relationship to the study drug was not ruled out for eczema nummular and hypersensitivity in the alirocumab group (1 subject each), and the study drug was discontinued. No deaths occurred. The study drug was discontinued due to systemic allergy-related AEs in 0.6% (14 of 2476) of subjects in the alirocumab group and 0.2% (2 of 1276) of subjects in the placebo group. In the foreign phase II study (Study DFI11565), which was not included in the pooled data, 1 subject in the alirocumab 300 mg Q4W group discontinued the study drug due to hypersensitivity vasculitis (verbatim term, leukocytoclastic vasculitis).

Table 39. Incidences of AEs related to systemic allergy (pooled data from placebo-controlled studies)

	Placebo (N = 1276)	Alirocumab (N = 2476)
Systemic allergy related AEs	7.8 (99)	8.6 (213)
Pruritus	0.4 (5)	1.1 (28)
Seasonal allergy	0.5 (6)	0.8 (21)
Dermatitis contact	0.2 (3)	0.4 (9)
Drug hypersensitivity	<0.1 (1)	0.3 (8)
Urticaria	<0.1 (1)	0.3 (7)

% (N)

Table 40 shows the incidences of AEs related to systemic allergy (all AEs combined and AEs occurred more frequently in the alirocumab group than in the ezetimibe group [AEs reported in ≥0.3% of subjects in the alirocumab group]) based on the pooled data from ezetimibe-controlled studies. SAEs related to systemic allergy were rare and were reported in 1 subject (hypersensitivity) in the alirocumab group and 2 subjects (hypersensitivity, urticaria) in the ezetimibe group. None of these events were fatal. The incidence of AEs leading to the discontinuation of the study drug was higher in the alirocumab group (0.8%, 7 of 864) than in the ezetimibe group (0.3%, 2 of 618). No relationship was found between the systemic allergy-related AEs and ADA-positive status.

Table 40. Incidences of AEs related to systemic allergy
(pooled data from ezetimibe-controlled studies)

	Ezetimibe (N = 618)	Alirocumab (N = 864)
AEs related to systemic allergy	5.3 (33)	6.8 (59)
Rash	1.0 (6)	1.4 (12)
Pruritus	0.5 (3)	0.8 (7)
Eczema	0.5 (3)	0.6 (5)
Dermatitis contact	0.2 (1)	0.5 (4)
Asthma	0.2 (1)	0.3 (3)
Hypersensitivity	0.2 (1)	0.3 (3)
Dermatitis	0 (0)	0.3 (3)

% (N)

PMDA's view:

In the foreign clinical studies, systemic allergy-related AEs occurred more frequently in the alirocumab group than in the control group, with some serious events such as leukocytoclastic vasculitis. Therefore, attention must be paid to the risk of systemic allergy-related events during treatment with alirocumab, and this should be advised in the package insert. Details in the advice is to be finalized based on comments from the Expert Discussion. The Japanese clinical studies showed no trend towards a higher incidence of systemic allergy-related AEs in the alirocumab group than that in the placebo group, and no SAEs or AEs leading to the discontinuation of the study drug were reported. However, since these evaluations were performed in a limited number of subjects, data on the risk of systemic allergy-related events in Japanese patients should be continuously collected through post-marketing surveillance.

7.R.5.4 Creatine kinase increased and musculoskeletal AEs

The applicant's explanation about musculoskeletal AEs during treatment with alirocumab:

In the Japanese phase III study (Study EFC13672), musculoskeletal AEs (PTs: myalgia, muscle spasms, muscle twitching, muscle tightness, myofascial spasm, limb discomfort, musculoskeletal discomfort, musculoskeletal pain, pain in extremity, back pain, muscular weakness, musculoskeletal stiffness, muscle contracture, muscle fatigue, muscle contractions involuntary) were reported in 18.2% (26 of 143) of subjects in the alirocumab group and 18.1% (13 of 72) of subjects in the placebo group. The incidence of back pain in the alirocumab group was ≥10% and higher than in the placebo group by ≥2% (12.6% [18 of 143] of subjects in the alirocumab group and 5.6% [4 of 72] of subjects in the placebo

group). Mild creatine kinase (CK) increased and possibly clinically significant abnormality (PCSA) were observed in 3.5% (5 of 143) of subjects in the alirocumab group, and only 1 of these events was considered related to the study drug. All CK increased resolved within approximately 1 month, and the maximum CK level was within the range of 3- to 10-fold the upper limit of normal (ULN) (men, 18-198 IU/L; women, 18-169 IU/L) in all subjects.

According to the pooled results from placebo-controlled studies included in the pooled global safety data,[7)] musculoskeletal AEs were observed in 15.1% (373 of 2476) of subjects in the alirocumab group and 15.4% (197 of 1276) of subjects in the placebo group. The pooled results from ezetimibe-controlled studies show that these AEs were observed in 13.8% (119 of 864) of subjects in the alirocumab group and 16.5% (102 of 618) of subjects in the ezetimibe group. The incidences of individual AEs in the alirocumab group were similar to those in the control group. In the alirocumab group, there was no specific safety concerns about the overall musculoskeletal AEs, serious musculoskeletal AEs, and musculoskeletal AEs leading to the discontinuation of the study drug. CK increased was observed in 1.2% (15 of 1276) of subjects in the placebo group and 0.9% (22 of 2476) of subjects in the alirocumab group in the pooled results from placebo-controlled studies. In the pooled results from ezetimibe-controlled studies, these AEs were observed in 0.8% (5 of 618) of subjects in the ezetimibe group and 0.8% (7 of 864) of subjects in the alirocumab group. In the alirocumab group, the maximum CK level ranged from 3- to ≤10-fold the ULN in most subjects except 3 subjects, in whom the CK levels were >10-fold the ULN. A causal relationship with the study drug was ruled out for CK increased in these 3 subjects, and the event was not accompanied by symptoms of musculoskeletal events. The frequency of CK increased >10-fold the ULN in the alirocumab group was lower than that in the placebo and ezetimibe groups, and most episodes of CK increased resolved over approximately 1 month.

These results showed no potential safety risks of alirocumab in terms of causing or increasing musculoskeletal AEs including CK increased. However, alirocumab is co-administered with a statin, and statins are well known to cause musculoskeletal AEs including CK increased. Patients should be carefully monitored for musculoskeletal AEs in routine physical examinations. The package insert of alirocumab gives the following advice to healthcare professionals in the "Important Precautions" section: "Prior to treatment, the descriptions of 'Contraindications,' 'Careful Administration,' 'Important Precautions,' and 'Clinically significant adverse reactions,' etc. in the package insert of the concomitant HMG-CoA reductase inhibitor should be read."

PMDA's view:

The Japanese and foreign clinical studies showed no trend towards higher incidences of CK increased and musculoskeletal AEs in the alirocumab group than in the placebo and ezetimibe groups, and most subjects used a concomitant statin in these clinical studies. Given these facts, CK increased and musculoskeletal AEs in the alirocumab group cannot necessarily be determined to have been caused by alirocumab. At the same time, in the Japanese clinical studies, the maximum CK levels after the administration of alirocumab was within the range of ≤10-fold the ULN. Nevertheless, the data were

derived from a limited number of subjects, and CK increased to >10-fold the ULN in the foreign clinical studies, suggesting the need of attention to the events. Post-marketing data on musculoskeletal AEs and changes in CK should be collected.

7.R.5.5 Antibody production

The applicant explanation about the production of antibodies during treatment with alirocumab:
In the Japanese phase II study (Study DFI12361), ADA was detected in 8 subjects in the alirocumab groups (1 in the 50 mg group, 4 in the 75 mg group, and 3 in the 150 mg group), and neutralizing antibody was detected in 1 subject in the 150 mg group. In the Japanese phase III study (Study EFC13672), ADA was detected in 2.8% (4 of 143) of subjects in the alirocumab group and 1.4% (1 of 72) of subjects in the placebo group. No neutralizing antibody was detected, and there were no specific safety concerns in ADA-positive subjects.

In the pooled analysis of 10 foreign phase III studies,[2)] ADA was noted in 4.8% (147 of 3033) of subjects in the alirocumab group and 0.6% (10 of 1708) of subjects in the control group. In the alirocumab group, 26.5% (39 of 147) of ADA-positive subjects were judged to have sustained ADA (tested positive for 2 samples collected consecutively at an interval of ≥12 weeks), with the median time to antibody expression of 12 weeks. The incidence of AEs was 76.2% (112 of 147) in ADA-positive subjects and 75.9% (2191 of 2886) in ADA-negative subjects. AEs occurring more frequently in ADA-positive subjects than in ADA-negative subjects (AEs reported in ≥4% of subjects and showing a difference of ≥2% between the treatment groups) were nasopharyngitis (12.2% [18 of 147] of ADA-positive subjects and 10.1% [291 of 2886] of ADA-negative subjects), injection site reaction (10.2% [15 of 147] and 5.8% [167 of 2886]), back pain (7.5% [11 of 147] and 4.0% [116 of 2886]), and headache (6.8% [10 of 147] and 4.5% [129 of 2886]). The incidence of AEs related to systemic allergy in the alirocumab group was 8.8% (13 of 147) in ADA-positive subjects and 8.2% (238 of 2886) in ADA-negative subjects. Hypersensitivity was reported as the SAE related to systemic allergy in 2 ADA-positive subjects. The incidence of injection site reaction was 10.2% (15 of 147) in ADA-positive subjects and was higher than in ADA-negative subjects (5.8%, 167 of 2886). Most injection site reactions were mild and transient. Neutralizing antibody was detected in 1.2% (36 of 3033) of subjects in the alirocumab group, but there was no noteworthy safety concerns including systemic allergy-related AEs and immune disorders.

Generally, no clinically significant difference was found in safety in ADA-positive subjects as compared with ADA-negative subjects. The incidence of injection site reaction in neutralizing antibody-positive subjects(11.1%, 4 of 36) was higher than that in ADA-negative subjects (5.8%, 167 of 2866) but was close to that in ADA-positive subjects who tested negative for neutralizing antibody (8.4%, 11 of 131). In the Japanese and foreign clinical studies, ADA expression did not affect the LDL-C lowering effect of alirocumab, and the same observation was made in subjects tested positive for neutralizing antibody. These results show no need to measure antibodies in general clinical settings. The “Other precautions” section of the package insert provides data on antibodies obtained in clinical studies.

PMDA's view:

As discussed by the applicant, although the possibility remains that alirocumab may induce antibody production, the Japanese and foreign clinical studies showed low expression of ADA and no data suggestive of decreased efficacy of alirocumab in ADA-positive subjects. The safety analyses did not show clinically significant increase in AEs related to allergic reactions due to antibody production, other than injection site reaction. In ADA-positive subjects, most injection site reactions were transient and had resolved, despite a tendency to occur more frequently than in ADA-negative subjects. The percentage of ADA-positive subjects who discontinued alirocumab did not tend to be markedly higher than that in ADA-negative subjects. Taking these results into consideration, there is no need for specific measures against antibody production at this point. Although neutralizing antibodies were found in 20% to 30% of ADA-positive subjects, the efficacy of alirocumab did not tend to decrease and, therefore, there is no need for specific measures against neutralizing antibody expression as well. There is less need for regular measurement of antibodies in clinical settings at this point, considering its clinical significance. If a serious allergic reaction occurs during treatment with alirocumab or if the efficacy of alirocumab is adversely affected in long-term treatment, the necessity of regular antibody measurement should be discussed. Because the relationships between ADA expression and the efficacy and safety of alirocumab have been evaluated in only a limited number of subjects, particularly in Japanese, relevant post-marketing data should be further collected, and new findings should be communicated to healthcare professionals as necessary.

7.R.5.6 Effect on cognitive function

The applicant's explanation:

Neurocognitive events categorized into MedDRA HLGTs of "deliria (including confusion)," "cognitive and attention disorders and disturbances," "dementia and amnestic conditions," "disturbances in thinking and perception," and "mental impairment disorders" were tabulated. In the Japanese phase II study (Study DFI12361) and Japanese phase III study (Study EFC13672), no subject experienced neurocognitive events.

Table 41 shows neurocognitive AEs in the pooled results from placebo-controlled studies included in the pooled global safety data[7)].

Table 41. Neurocognitive AEs (pooled data from placebo-controlled studies)

	Placebo (N = 1276)	Alirocumab (N = 2476)
Neurocognitive events	0.7 (9)	0.8 (21)
Confusional state	<0.1 (1)	0.2 (6)
Memory impairment	<0.1 (1)	0.2 (5)
Amnesia	0.2 (2)	0.2 (5)
Dementia	0.2 (2)	<0.1 (1)
Transient global amnesia	<0.1 (1)	<0.1 (1)
Disturbance in attention	<0.1 (1)	<0.1 (2)
Confusion postoperative	0 (0)	<0.1 (1)
Disorientation	0 (0)	<0.1 (1)
Frontotemporal dementia	0 (0)	<0.1 (1)
Delirium	<0.1 (1)	0 (0)
Dementia Alzheimer's type	<0.1 (1)	0 (0)

% (N)

The outcomes of these AEs were “resolved” (10 subjects) and “not resolved” (11 subjects) in the 21 subjects in the alirocumab group, and “resolved” (3 subjects), “resolved with sequelae” (1 subject), “not resolved” (4 subjects), and “death” (1 subject) in the 9 subjects in the placebo group. No marked difference was noted in the outcomes of AEs between the alirocumab and placebo groups.

Table 42 shows neurocognitive AEs in the pooled results from ezetimibe-controlled studies.

Table 42. Neurocognitive AEs (pooled data from ezetimibe-controlled studies)

	Ezetimibe (N = 618)	Alirocumab (N = 864)
Neurocognitive events	1.0 (6)	0.9 (8)
Memory impairment	0 (0)	0.3 (3)
Confusional state	0.3 (2)	0.2 (2)
Amnesia	0.3 (2)	0.1 (1)
Aphasia	0 (0)	0.1 (1)
Dementia Alzheimer's type	0 (0)	0.1 (1)
Hallucination	0 (0)	0.1 (1)
Disturbance in attention	0.3 (2)	0 (0)
Transient global amnesia	0.2 (1)	0 (0)

% (N)

The outcomes of these AEs were “resolved” (5 subjects) and “not resolved” (3 subjects) in the 8 subjects in the alirocumab group, and “resolved” (3 subjects) and “not resolved” (3 subjects) in the 6 subjects in the ezetimibe group.

These results do not raise any safety concerns over neurocognitive events associated with alirocumab. However, in light of an assessment of neurocognitive events to be conducted in response to a request made by FDA on the basis of the safety data of other lipid-lowering drugs, post-marketing data on these events will be collected.

PMDA’s view on AEs related to cognitive function occurring during treatment with alirocumab:

In the Japanese phase III study (Study EFC13672), no obvious neurocognitive event was observed. The pooled global safety data did not suggest the clear possibility that alirocumab increases neurocognitive events as compared with placebo or ezetimibe. In the foreign long-term study (Study LTS11717), on the other hand, neurocognitive events were observed more frequently in the alirocumab group than in the placebo group (1.2% [18 of 1550] of subjects in the alirocumab group, 0.5% [4 of 788] of subjects in the placebo group). Cholesterol is essential for cerebral nerve activity. Much remains unclear about long-term effects of alirocumab on cognitive functions because of inadequate investigation with limited subjects and time given. Given this situation, the possibility cannot be completely ruled out that the cholesterol-lowering effect of alirocumab affect neurological functions in the long term. For these reasons, data on the effect on cognitive functions during long-term treatment with alirocumab should be continuously collected after the market launch.

7.R.5.7 Effect on eyes

The applicant's explanation about a relationship between alirocumab and ophthalmologic events:
Ophthalmologic events were tabulated according to AEs categorized into SMQ of "optic nerve disorder" (narrow and broad), "retinal disorder" (narrow), and "corneal disorder" (narrow). In the Japanese phase III study (Study EFC13672), ophthalmologic AEs occurred in 2.8% of subjects (4 subjects; diabetic retinopathy, retinal vein occlusion, vitreous haemorrhage, and hemianopia homonymous in 1 subject each) in the alirocumab group and 2.8% of subjects (2 subjects; diabetic retinopathy in both subjects) in the placebo group. The event in 1 subject in the alirocumab group (vitreous haemorrhage) was judged to be serious, but a relationship to alirocumab was ruled out for the event.

According to the placebo-controlled study data included in the pooled global safety data[7)], ophthalmologic events occurred in 1.8% (44 of 2476) of subjects in the alirocumab group and 1.4% (18 of 1276) of subjects in the placebo group. Frequently observed were non-specific events (visual acuity reduced, visual impairment, and colour vision tests abnormal) and retinal disorders (vitreous floaters, vitreous detachment, and retinal detachment), which are common in the age group of the target population. Serious ophthalmologic events were observed in 0.3% of subjects (7 subjects; demyelination, optic neuritis, retinal artery embolism, retinal detachment, retinal haemorrhage, retinal vein thrombosis and vitreous detachment, and visual impairment in 1 subject each) in the alirocumab group and 0.2% of subjects (3 subjects; retinal vein occlusion in 2 subjects, retinal vein occlusion and diabetic retinopathy in 1 subject) in the placebo group. Ophthalmologic events led to the discontinuation of the study drug in 2 subjects in the alirocumab group (optic neuritis and vitreous floaters in 1 subject each) and none in the placebo group. In the pooled results from ezetimibe-controlled studies, ophthalmologic events were observed in 0.8% (7) of subjects in the alirocumab group and 0.5% (3) of subjects in the ezetimibe group. Serious ophthalmologic events were observed in 1 subject in the alirocumab group (retinal detachment) and none in the ezetimibe group. No ophthalmologic event led to the discontinuation of the study drug in any treatment groups. None of these ophthalmologic events were of safety concerns.

PMDA's view:
The Japanese clinical study results did not show a trend that ophthalmologic events occurred more frequently in the alirocumab group than in the placebo group. On the other hand, the pooled global safety data showed that ophthalmologic events tended to occur more frequently in the alirocumab group than in the placebo group. In the foreign long-term study (Study LTS11717), the incidence of ophthalmologic events was higher in the alirocumab group (2.5%, 38 of 1550 subjects) than in the placebo group (1.9%, 15 of 788 subjects). However, a causal relationship between alirocumab and ophthalmologic events is not clear, and the results did not indicate the need for ophthalmologic monitoring. Nevertheless, long-term ophthalmologic effects of alirocumab remain unclear due to inadequate investigation with limited subjects and time given. Ophthalmologic events should be, therefore, investigated in a long term through post-marketing surveillance, etc.

7.R.5.8 Effect on hormones
PMDA requested the applicant to explain alirocumab's cholesterol lowering effect on steroid hormones.

The applicant's explanation:
The Japanese phase III study (Study EFC13672) did not required to determine adrenal or gonadal hormones. AEs related to adrenal or gonadal hormones under the System Organ Classes (SOCs) of "endocrine disorders," "reproductive system and breast disorders," and "investigations" were rare in the alirocumab and placebo groups, and none of the relevant AEs in the alirocumab group were serious or led to the discontinuation of the study drug. Of subjects with LDL-C levels of <25 mg/dL at 2 consecutive measurements, 1 subject experienced prostatomegaly. A causal relationship to alirocumab was ruled out for the event.

In the foreign long-term study (Study LTS11717), cortisol, adrenocorticotropic hormone (ACTH), luteinizing hormone, follicle-stimulating hormone, total testosterone (men), and estradiol (women of child bearing potential not on hormonal contraceptives) were determined to evaluate the effect of alirocumab on adrenal or gonadal hormones including related AEs. The proportions of subjects with abnormal adrenal or gonadal hormones were similar between the alirocumab and placebo groups. In the alirocumab group, blood cortisol decreased and erectile dysfunction occurred in 1 subject each, whose LDL-C levels were <25 mg/dL at 2 consecutive measurements.

These results showed no significant difference in the changes in test values related to adrenal or gonadal hormones between the alirocumab and placebo groups or no tendency suggesting the possibility of cortisol deficiency or gonadal insufficiency. However, because safety data on gonadal hormones from the Japanese clinical studies are limited, relevant post-marketing data will be further collected.

PMDA's view:
In the foreign long-term study (Study LTS11717), although in an extremely small number of subjects, hormone levels did not tend to suggest any obvious effect of alirocumab on steroid hormones. In the

Japanese and foreign clinical studies, the incidence of sex hormone-related AEs related was not particularly high in the alirocumab group [see Section "7.R.5.1 Excessive decrease in LDL-C"]. Therefore, the conduct of specific tests is not required at present. However, the available data show the effect of decreased LDL-C levels on steroid hormones only in the short-term use of alirocumab in a limited number of subjects. Unknown long-term effect of decreased LDL-C should be evaluated through post-marketing surveillance, etc.

7.R.5.9 Risk of hepatic impairment

Alirocumab's mechanism of action may adversely affect the liver. PMDA requested the applicant to explain the occurrence of AEs related to hepatic impairment and abnormal laboratory findings, including increases in AST and ALT, and the results of imaging tests in the Japanese and foreign clinical studies. PMDA also requested the applicant to explain its view on the risk of hepatic adverse drug reactions of alirocumab.

The applicant's explanation:

The Japanese clinical studies and foreign phase III studies (8 of 10 studies) used alirocumab as an add-on drug to statin therapy. The pooled results from placebo-controlled studies included in the pooled data from 10 foreign phase III studies[2)] show that most subjects used a concomitant statin, and the pooled results from ezetimibe-controlled studies show that approximately 75% to 80% of subjects used a concomitant statin. In the foreign clinical studies, approximately 40% of subjects in any treatment groups had baseline BMI of ≥30 kg/m^2 and possibly had fatty liver. In the Japanese phase II study (Study DFI12361), liver disorder was one of AEs occurred in 1 subject (with concomitant atorvastatin 5 mg) in the alirocumab 50 mg Q2W group, in whom ALT increased to 3.8-fold the ULN (4.4-fold the baseline value) on Days 85 and 125 (within the follow-up period), and AST also increased to 3.96-fold the ULN. These events were judged to be causally related to the study drug and atorvastatin, and resolved without treatment. In the Japanese phase III study (Study EFC13672), hepatic function disorder was reported as an AE in 5.6% (8 of 143) of subjects in the alirocumab group and 2.8% (2 of 72) of subjects in the placebo group. None of these events were SAEs or AEs leading to the discontinuation of the study drug. Hepatic impairment-related AEs with a suspected causal relationship to the study drug were observed in 0.7% (1) of subjects in the alirocumab group and 1.4% (1) of subjects in the placebo group. Table 43 shows the percentage of subjects with PCSA in the liver function test in the Japanese phase III study (Study EFC13672). These events occurred frequently in subjects who had hepatic impairment at baseline. No subject met the criteria of Hy's law (ALT of >3-fold the ULN and total bilirubin of >2-fold the ULN).

Table 43. PCSA in liver function test at Week 52 (Study EFC13672)

	Placebo (N = 72)	Alirocumab (N = 143)
ALT increased to >3-fold ULN	1.4 (1)	3.5 (5)
ALT increased to >5-fold ULN	0 (0)	1.4 (2)
AST increased to >3-fold ULN	1.4 (1)	1.4 (2)
AST increased to >5-fold ULN	0 (0)	1.4 (2)
AST increased to >10-fold ULN	0 (0)	0.7 (1)

% (N)

According to the pooled results from placebo-controlled studies included in pooled global safety data,[7] AEs related to hepatic impairment (categorized into the SMQ of "liver disorder") were observed in 2.5% (61 of 2476) of subjects in the alirocumab group and 1.8% (23 of 1276) of subjects in the placebo group. Major AEs were ALT increased (1.1% [28] of subjects in the alirocumab group and 0.7% [9] of subjects in the placebo group), gamma-glutamyl transpeptidase increased (0.4% [10] and 0.2% [3]), hepatic enzyme increased (0.3% [7] and <0.1% [1], AST increased (0.2% [5] and 0% [0]), and hepatic steatosis (0.2% [4] and 0.3% [4]). SAEs occurred in <0.1% of subjects (hepatic steatosis in 1 subject) in the placebo group and 0.3% (8) of subjects (ALT increased in 3 subjects; hepatitis A, hepatitis alcoholic, hepatocellular injury, hepatic enzyme increased, and international normalised ratio increased in 1 subject each) in the alirocumab group. No AE resulted in death. AEs led to the discontinuation of the study drug in 0.4% (9) of subjects (ALT increased in 4 subjects; hepatic enzyme increased in 2 subjects; hepatitis alcoholic, gamma-glutamyl transpeptidase increased, and transaminases increased in 1 subject each) in the alirocumab group and 0.2% (2) of subjects (hepatic steatosis and ALT increased in 1 subject each) in the placebo group. According to the pooled results from ezetimibe-controlled studies, AEs related to hepatic impairment occurred in 1.9% (16 of 864) of subjects in the alirocumab group and 2.3% (14 of 618) of subjects in the ezetimibe group. Major AEs were ALT increased (0.6% [5] of subjects in the alirocumab group and 0.8% [5] of subjects in the ezetimibe group), and hepatic steatosis (0% [0] and 0.6% [4]). A SAE occurred in 1 subject (hepatitis E) in the alirocumab group. AEs led to the discontinuation of the study drug in 0.5% (4) of subjects (ALT increased [1], transaminases increased [1], concurrent transaminases increased and hepatic lesion [1], and concurrent ALT increased and AST increased [1] in the alirocumab group, and 0.2% of subjects (ALT increased [1]) in the ezetimibe group.

The incidence of abnormal liver function test, namely, PCSA of ALT increased, did not differ among the treatment groups in the pooled results from placebo-controlled studies. ALT increased >3-fold the ULN in 1.7% (41 of 2455) of subjects in the alirocumab group and 1.4% (18 of 1266) of subjects in the placebo group. According to the pooled results from placebo-controlled studies, ALT increased >3-fold the ULN and total bilirubin increased >2-fold the ULN in 1 subject in the alirocumab group and 2 subjects in the placebo group. Although these subjects met the criteria of Hy's law, they had other causes of the abnormality (hepatitis A, cholangitis, or cholecystitis acute). In the pooled results from ezetimibe-controlled studies, ALT increased >3-fold the ULN in 9 subjects in the alirocumab group and 1 subject in the ezetimibe group. The 9 subjects in the alirocumab group had an explicable causes or confounding factors identified or had their ALT returned to normal during the treatment with alirocumab. No

difference was noted in the incidence of PCSA of AST increased between the groups of pooled results from placebo-controlled studies (1.1% [28 of 2455] of subjects in the alirocumab group and 1.4% [18 of 1266] of subjects in the placebo group). In the pooled results from ezetimibe-controlled studies, AST >3-fold the ULN was observed in 1.2% (10 of 849) of subjects in the alirocumab group and none in the ezetimibe group.

In the foreign clinical studies, some subjects underwent imaging (mainly ultrasound) for the diagnosis of hepatic impairment or abnormal liver function tests. The comprehensive review of hepatic function-related AEs, and PCSA and mean over-time changes in the liver function tests revealed no difference in the incidence of hepatic function disorder and liver function test abnormal between the alirocumab and control groups (placebo group in particular) and suggested no potential risk of hepatic impairment associated with alirocumab.

PMDA's view:
The currently available data from the Japanese and foreign clinical studies provide no evidence of alirocumab-induced serious hepatic impairment that met the criteria of Hy's law. Because most of these clinical studies used alirocumab with a statin, hepatic impairment may have been attributable to the statin. However, in Japan, abnormal liver function test tended to be observed more frequently in the alirocumab group than in the placebo group. Outside Japan, serious hepatic function disorders or hepatic function disorders led to the discontinuation of the study drug more frequently in the alirocumab group than in the control group. These results suggest the possibility that alirocumab caused hepatic function disorders. Therefore, patients must be closely monitored for these events, and appropriate precautionary advice should be given in the package insert. The descriptions of the advice will be finalized in light of the comments from the Expert Discussion.

7.R.5.10 Administration of alirocumab to patients with hepatic impairment
PMDA requested the applicant to explain the safety of alirocumab in patients with hepatic diseases such as hepatic cirrhosis and nonalcoholic fatty liver disease (NAFLD) and the possibility of use of alirocumab in patients with severe hepatic impairment.

The applicant's explanation:
The Japanese and foreign phase III studies excluded patients with ALT or AST levels of >3-fold the ULN. Patients with hepatic disease were included only when their baseline liver function had little change from screening. Patients were excluded from the studies if tested positive for hepatitis B antigen or hepatitis C antibody.

In the Japanese phase III study (Study EFC13672), 24.5% (35 of 143) of subjects in the alirocumab group and 22.2% (16 of 72) of subjects in the placebo group had ongoing hepatic impairment at baseline. All subjects were receiving a statin as basic therapy, and approximately 70% of subjects had diabetes

mellitus. Table 44 shows the incidences of AEs by presence of hepatic impairment. The incidences were similar between both populations.

Table 44. Incidences of AEs by the presence of hepatic impairment (Study EFC13672)

	Patients with hepatic impairment		Patients with normal liver function	
	Placebo (N = 16)	Alirocumab (N = 35)	Placebo (N = 56)	Alirocumab (N = 108)
AEs	75.0 (12)	65.7 (23)	58.9 (33)	75.0 (81)
SAEs	12.5 (2)	8.6 (3)	3.6 (2)	2.8 (3)
AEs that led to the discontinuation of study drug	6.3 (1)	8.6 (3)	1.8 (1)	2.8 (3)

% (N)

Tables 45 and 46 show the incidences of AEs by presence of hepatic impairment in the pooled global safety data.[7)] Although the hepatic impairment-related AEs tended to occur more frequently in patients who had hepatic impairment at baseline than in patients who did not, there was no significant difference in the incidence of overall AEs between the alirocumab and control groups regardless of the presence of hepatic impairment.

Table 45. Incidences of AEs by the presence of hepatic impairment (pooled data from placebo-controlled studies)

	Patients with hepatic impairment		Patients with normal liver function	
	Placebo (N = 57)	Alirocumab (N = 125)	Placebo (N = 1219)	Alirocumab (N = 2351)
AEs	73.7 (42)	75.2 (94)	76.5 (933)	75.8 (1782)
SAEs	26.3 (15)	12.8 (16)	13.7 (167)	13.8 (324)
AEs that led to the discontinuation of study drug	7.0 (4)	5.6 (7)	5.0 (61)	5.3 (124)

% (N)

Table 46. Incidence of AEs by the presence of hepatic impairment (pooled data from ezetimibe-controlled studies)

	Patients with hepatic impairment		Patients with normal liver function	
	Ezetimibe (N = 35)	Alirocumab (N = 58)	Ezetimibe (N = 583)	Alirocumab (N = 806)
AEs	74.3 (26)	62.1 (36)	67.8 (395)	70.8 (571)
SAEs	17.1 (6)	12.1 (7)	10.8 (63)	13.2 (106)
AEs that led to the discontinuation of study drug	11.4 (4)	8.6 (5)	9.1 (53)	8.7 (70)

% (N)

These results raised no special hepatic safety concerns following the administration of alirocumab to patients with hepatic impairment. Because the currently available clinical data do not indicate concerns about hepatic ADRs of alirocumab, precautionary advice on use in patients with severe hepatic impairment is not necessary in the package insert. However, data of this patient population will be further collected after the market launch.

PMDA's view:

As described in Section "6.R.2 Administration of alirocumab to patients with hepatic impairment," from a PK perspective, dose adjustment is not necessary especially for patients with mild or moderate hepatic impairment at this point. However, considering the limited data because of the criteria of the Japanese and foreign phase III studies that excluded patients with ALT or AST levels of >3-fold the ULN, alirocumab should be administered carefully to patients with severe hepatic impairment. Healthcare professionals should be informed of the lack of clinical experience in the use of alirocumab in this patient population. Data on the safety of alirocumab in patients with hepatic impairment should be further collected after the market launch.

7.R.5.11 Diabetes mellitus and increased blood glucose level

The applicant's explanation on the diabetic risk following the administration of alirocumab:

In the Japanese phase II study (Study DFI12361), the proportion of patients with PCSA of fasting blood sugar levels was similar among all treatment groups, and no obvious increase from baseline was noted. The observed HbA1c levels and their changes from baseline were similar among all treatment groups, and no obvious change from baseline was noted. In the Japanese phase III study (Study EFC13672), there was no clinically significant difference in changes from baseline in fasting blood sugar levels and the proportion of subjects with PCSA among all treatment groups. Table 47 shows changes in HbA1c from baseline at Weeks 24 and 52. No clinically significant difference was noted among the treatment groups regardless of whether the subject had diabetes mellitus at baseline.

Table 47. Changes from baseline HbA1c at Weeks 24 and 52
(Study EFC13672, safety analysis set)

		Week 24	Week 52
Overall	Placebo	−0.02 ± 0.37 (70)	0.15 ± 0.56 (65)
	Alirocumab	−0.01 ± 0.55 (137)	0.05 ± 0.59 (127)
Patients with no history of diabetes mellitus	Placebo	−0.02 ± 0.17 (29)	0.09 ± 0.15 (27)
	Alirocumab	0.04 ± 0.17 (37)	0.12 ± 0.16 (33)
Patients with diabetes mellitus	Placebo	−0.01 ± 0.46 (41)	0.20 ± 0.72 (38)
	Alirocumab	−0.03 ± 0.64 (100)	0.03 ± 0.68 (94)

Mean ± SD (N)

In the Japanese phase III study (Study EFC13672), the percentage of subjects with PCSA of HbA1c (HbA1c > 8%) was higher in the alirocumab group (22.5%, 32 of 142 subjects) than in the placebo group (12.5%, 9 of 72 subjects). The result was possibly attributable to the higher proportion of subjects with diabetes mellitus in the alirocumab group (72.9%, 105 of 144 subjects) than in the placebo group (59.7%, 43 of 72 subjects) and the higher proportion of subjects with a baseline HbA1c of ≥6.5% in the alirocumab group (59.7%, 86 of 144 subjects) than in the placebo group (44.4%, 32 of 72 subjects).

Table 48 shows the incidences of PCSA of fasting blood sugar levels. The incidences were summarized by presence or absence of diabetes mellitus and alirocumab dose using the pooled results from placebo-controlled studies and those from ezetimibe-controlled studies included in the pooled global safety data.[7]

No difference was noted in the incidence of PCSA of fasting sugar levels between alirocumab and placebo regardless of the presence or absence of diabetes mellitus. In a comparison of alirocumab versus ezetimibe, the incidence of PCSA was slightly higher in the alirocumab group than in the ezetimibe group regardless of the presence or absence of diabetes mellitus. Considering the shorter durations of the ezetimibe-controlled studies and the similar in the incidence between the alirocumab group and the placebo group in the pooled results from placebo-controlled studies, there was no clinically significant difference between the treatment groups.

No significant over-time change was observed in HbA1c up to Week 52 (up to Week 24 in the pooled ezetimibe-controlled studies).

Table 48. Incidence of PCSA of fasting blood sugar level by diabetes mellitus
(Pooled data from placebo-controlled studies and ezetimibe-controlled studies)

	Diabetic patients			Non-Diabetic patients		
	Control	Alirocumab 75 mg Q2W	Alirocumab 150 mg Q2W	Control	Alirocumab 75 mg Q2W	Alirocumab 150 mg Q2W
Pooled placebo-controlled studies	71.2 (255/358)	60.8 (62/102)	76.0 (450/592)	9.6 (86/895)	5.7 (22/383)	10.5 (142/1346)
Pooled ezetimibe-controlled studies	62.2 (115/185)	72.1 (158/219)	81.1 (43/53)	6.9 (29/419)	9.7 (43/442)	10.2 (13/127)

% (Number of subjects with PCSA/Number of subjects analyzed)

AEs related to diabetes mellitus and diabetic complications were tabulated based on AEs classified into the MedDRA HLGT of “diabetic complications” and HLTs of “diabetes mellitus (including subtypes)” and “carbohydrate tolerance analyses (including diabetes)” (excluding the PT of “blood glucose decreased” and including the PT of “hyperglycaemia”). No AE related to diabetes mellitus or diabetic complications was reported in the Japanese phase II study (Study DFI12361). In the Japanese phase III study (Study EFC13672), 72.9% (105 of 144) of subjects in the alirocumab group and 59.7% (43 of 72) of subjects in the placebo group had diabetes mellitus, and diabetic AEs occurred in 14.7% (21) of subjects (diabetes mellitus aggravated in 19 subjects, preproliferative diabetic retinopathy aggravated in 1 subject, and HbA1c increased in 1 subject) in the alirocumab group and 9.7% (7) of subjects (diabetes mellitus aggravated in 4 subjects [including concurrent diabetic neuropathy in 1 subject], diabetic retinopathy in 2 subjects, and type 2 diabetes mellitus in 1 subject) in the placebo group. All of these subjects except 1 with type 2 diabetes mellitus in the placebo group had diabetes mellitus. All of 21 subjects in the alirocumab group and 5 of 7 subjects in the placebo group had a baseline HbA1c of ≥6.5%. The study drug was discontinued due to aggravated diabetes mellitus in 1 subject in the alirocumab group, but a causal relationship to alirocumab was ruled out for the event.

According to the pooled results from placebo-controlled studies included in the pooled global safety data[7)], diabetic AEs occurred in 4.2% (103 of 2476) of subjects in the alirocumab group and 3.8% (49 of 1276) of subjects in the placebo group. Major AEs (AEs reported in ≥0.5% of subjects in any treatment group) were diabetes mellitus (1.3% [32 subjects] in the alirocumab group and 1.1% [14

subjects] in the placebo group), type 2 diabetes mellitus (1.3% [31 subjects] and 0.9% [12 subjects]), diabetes mellitus inadequate control (0.5% [12 subjects] and 0.5% [7 subjects]), and hyperglycaemia (0.4% [9 subjects] and 0.5% [6 subjects]). The incidences of SAEs related to diabetes mellitus were 0.2% (6 subjects) in the alirocumab group and 0.4% (5 subjects) in the placebo group. All of these subjects except 1 in the alirocumab group had diabetes mellitus at baseline. No deaths were reported. AEs led to the discontinuation of the study drug in <0.1% (2) of subjects in the alirocumab group and none in the placebo group. In the pooled results from ezetimibe-controlled studies, diabetic AEs were observed in 2.9% (25 of 864) of subjects in the alirocumab group and 3.6% (22 of 618) of subjects in the ezetimibe group. Major AEs (AEs reported in ≥0.5% of subjects in any treatment group) were diabetes mellitus (0.8% [7 subjects] in the alirocumab and 1.6% [10 subjects] in the ezetimibe group), type 2 diabetes mellitus (0.6% [5 subjects] and 0.3% [2 subjects]), hyperglycaemia (0.3% [3 subjects] and 0.5% [3 subjects]), and blood glucose increased (0.1% [1 subject] and 0.8% [5 subjects]). No SAEs or AEs leading to the discontinuation of the study drug occurred.

These results suggested no obvious risks such as abnormal glucose tolerance associated with the use of alirocumab, and precautionary advice on diabetes mellitus is not necessary in the package insert.

PMDA's view:

As revealed in the Japanese phase II study (Study DFI12361) and phase III study (Study EFC13672), except the tendency toward more frequent diabetic AEs in the alirocumab group than in the placebo group seen in the Japanese phase III study (Study EFC13672), there were no other findings suggestive of concerns over declined blood sugar level control in Japanese diabetic patients or increased blood sugar level in Japanese non-diabetic patients. In the foreign pooled results from placebo-controlled studies and ezetimibe-controlled study data, on the other hand, the incidence of PCSA of blood sugar levels tended to be higher in the alirocumab 150 mg Q2W group than in the control group of both diabetic and non-diabetic subjects. Furthermore, considering the more frequent PCSA of blood sugar levels in the alirocumab 150 mg Q2W group than in the 75 mg Q2W group in all subgroups, the risk of increased blood sugar levels following treatment with alirocumab cannot be ruled out. However, in light of the incidence of diabetic AEs in the pooled global safety data, there is no data clearly indicating a risk of increased blood sugar level associated with alirocumab at this point. Nevertheless, due to the mechanism of action of alirocumab, it cannot be denied that increased LDLR in pancreatic β cells may worsen glycemic control, and currently data on the effect of alirocumab on glucose tolerance in Japanese patients are limited. Relevant data should be further collected through post-marketing surveillance or other surveys.

7.R.5.12 Safety in patients infected with hepatitis C virus

PMDA requested the applicant to explain liver function and HCV load following the administration of alirocumab to HCV-positive patients (including asymptomatic carriers and hepatitis C patients), the appropriateness of treatment of HCV-positive patients with alirocumab, and the need for precautionary advice in the package insert.

The applicant's explanation:
According to *in vitro* data, the overexpression of non-secreted cell membrane-bound form of PCSK9 decreased the expression of CD81 on the hepatocyte surface. Based on this, the inhibition of PCSK9 is expected to increase CD81 expression levels and invasion of HCV into hepatocytes (*Hepatol*. 2009;50(1):17-24). Therefore, asymptomatic HCV carriers and chronic hepatitis C patients were excluded from the phase II and III studies of alirocumab.

However, alirocumab neither affected CD81 expression levels in hepatocytes nor changed any steps of the HCV replicative cycle in the non-clinical studies. Treatment with alirocumab, therefore, is unlikely to increase sensitivity to HCV infection, and precautionary advice especially on the use in HCV carriers and chronic hepatitis C patients is not necessary. Nevertheless, because these patient populations were excluded from the clinical studies, post-marketing data on safety, etc. in these patients will be collected.

PMDA's view:
Whether alirocumab increases the risk of causing or aggravating hepatitis C is unknown because HCV-positive patients were excluded from the Japanese and foreign clinical studies. However, to date, no significant safety concerns of other anti-PCSK9 antibody drugs have been identified in HCV-positive patients, and the restriction of the use of alirocumab in this patient population is thus not necessary. Nevertheless, an increasing risk of hepatitis C caused or aggravated by alirocumab cannot be denied theoretically. Thus the lack of clinical experience in treatment with alirocumab in HCV-positive patients should be communicated to healthcare professionals. Any new findings and safety issues raised from post-marketing surveillance or other surveys should be utilized to take necessary measures and provided to healthcare professionals in an appropriate manner.

7.R.5.13 Safety in long-term treatment
The applicant's explanation about alirocumab's safety in long-term treatment:
Table 49 shows the incidences of major AEs by timing of initial onset in the Japanese phase III study (Study EFC13672). The incidences tended to decrease over time from Week 36 in both the alirocumab and placebo groups. The incidences by timing of initial onset for AEs frequently reported up to Week 52 in the alirocumab group (nasopharyngitis and back pain) showed no special trend in either treatment group up to Week 52. While the proportion of subjects who experienced injection site reaction in the alirocumab group from Weeks 12 to 24 was higher than that from Weeks 0 to 12, the proportion tended to decrease over time from Week 24. There was no obvious increase in the incidences of other AEs, new frequently reported AEs, or clinically significant trend following long-term treatment with of alirocumab.

Table 49. Incidence of AEs by timing of onset in the Japanese phase III study (Study EFC13672)

		Weeks 0-12	Weeks 12-24	Weeks 24-36	Weeks 36-52
Number of subjects analyzed	Placebo	N = 72	N = 70	N = 70	N = 69
	Alirocumab	N = 143	N = 140	N = 137	N = 134
AEs	Placebo	16.1 (26)	19.4 (19)	15.2 (9)	9.4 (5)
	Alirocumab	25.3 (74)	17.6 (27)	24.2 (21)	9.1 (6)
Nasopharyngitis	Placebo	2.1 (4)	4.7 (8)	2.6 (4)	4.6 (8)
	Alirocumab	4.0 (15)	7.3 (23)	7.5 (19)	2.8 (8)
Back pain	Placebo	0.5 (1)	0.5 (1)	0.5 (1)	0.4 (1)
	Alirocumab	1.0 (4)	1.6 (6)	0.9 (3)	0.9 (4)
Injection site reaction	Placebo	1.0 (2)	0 (0)	0 (0)	0.4 (1)
	Alirocumab	1.3 (5)	2.8 (10)	0.9 (3)	0 (0)

%/person-month (N)

Table 50 shows the incidence of AEs by timing of initial onset in the pooled results from placebo-controlled studies included in the pooled global safety data.[7)] The incidence was high after the first dose up to Week 24 and tended to decrease from Week 24 in all treatment groups.

Table 50. Incidence of AEs by timing of onset in the pooled global safety data

		Weeks 0-24	Weeks 24-52	Weeks 52-78
Number of subjects analyzed	Placebo	N = 1174	N = 1086	N = 1012
	Alirocumab	N = 2318	N = 2140	N = 2011
AEs	Placebo	16.8 (735)	6.7 (143)	4.7 (39)
	Alirocumab	16.5 (1429)	6.2 (271)	4.4 (76)

%/person-month (N)

The incidences of individual AEs were also high after the first dose up to Week 24 and did not increase over time in long-term treatment. The incidences of AEs following treatment continued for ≥52 weeks were similar between the alirocumab group and the placebo group. Similar changes were observed in for AEs of special interest (local injection site reaction, allergic events, neurological events, neurocognitive events, musculoskeletal events, diabetes mellitus, hepatic impairment, ophthalmologic events) and other important AEs.

PMDA's view:

The results of the Japanese and foreign clinical studies did not show an increased incidence of AEs during long-term treatment with alirocumab or AEs specific to long-term treatment with alirocumab up to Week 52. However, treatment with alirocumab may be continued over several decades in clinical settings. Currently, safety of alirocumab in long-term treatment particularly that continues for ≥52 weeks, is unknown because of limited experience, and relevant data should be further collected after the market launch.

7.R.5.14 Self-injection

The applicant's explanation:

In the Japanese phase III study (Study EFC13672), 41 subjects in the alirocumab group and 21 subjects in the placebo group (approximately 30% of the entire subjects) performed self-injection. Approximately 90% of the total injections from Week 24 were self-injections in these subjects. Treatment compliance from Week 24 was favorable. Although 1 subject in the alirocumab group discontinued self-injection and switched to injection at the study site, the change was not due to safety reasons. The incidence of AEs from Week 24 in subjects who performed self-injection was 68.3% (28 of 41) of subjects in the alirocumab group and 57.1% (12 of 21) of subjects in the placebo group, and was lower than in subjects who did not perform self-injection (81.9% [77 of 94] of subjects in the alirocumab group and 77.6% [38 of 49] of subjects in the placebo group), and there was no AE clearly more frequent in subjects who performed self-injection. Accidental overdose of alirocumab 75 mg occurred 6 days after the previous dosing (on the day of last dose at Week 50) in 1 subject performing home self-injection, but no symptoms associated with overdose, requiring no therapeutic action. Injection site reaction occurring from Week 24 onward was reported in 7.3% (3 of 41) of subjects who performed self-injection and 3.2% (3 of 94) of subjects who did not perform self-injection in the alirocumab group, and 4.8% (1 of 21) of subjects who performed self-injection only in the placebo group. Regardless of whether self-injection was performed, these events were all mild and no significant difference was noted in the number of occurrences, duration of reaction, and symptoms related to injection site reaction. Of 3 subjects who experienced injection site reaction after self-injection in the alirocumab group, 1 subject discontinued the study drug due to injection site reaction and the event resolved in 5 days without medical treatment. The other 2 subjects continued self-injection up to Week 52. The above results showed no difference in the incidence of AEs regardless of self-injection of alirocumab and no obvious safety concern in subjects who performed self-injection. Patients who wish to undergo self-injection will be provided with guidance materials on the procedure and detailed instructions on the appropriate dosing interval and injection method, so that they will be familiarized with the procedure in advance. Therefore, alirocumab will be properly and safely self-injected by these patients.

PMDA's view:

In Japan, there is only 1 drug being approved for self-injection for the treatment of HC, and clinical experience in self-injection is insufficient. Alirocumab is meant for subcutaneous injection, but self-injection preparations have already been approved for other indications. Subcutaneous self-injection is thus not a highly novel procedure. In light of the results of the clinical study involving self-injection, alirocumab can be self-injected as long as appropriate instructions are given to patients. Adequate education of patients on drug control, injection procedures, and disposal of devices is necessary, and how to instruct patients appropriately should be further discussed.

7.R.6 Post-marketing investigations

The applicant's explanation:

A drug use-results survey will be performed using a central registration method (observation period, 2 years; number of subjects registered, 3300 subjects) in HC and FH patients at high risk of cardiovascular

events to evaluate the safety and efficacy of long-term clinical use of alirocumab. In this survey, data will be collected on the occurrence of immunogenicity, systemic hypersensitivity reaction, cataract, and neurocognitive disorders, and the drug's safety in chronic HCV carriers and hepatitis patients. Of the 3000 subjects to be included in the safety analysis set, patients with hepatic impairment and elderly patients (≥75 years) are estimated to count ≥300, which is considered a sufficient sample size to evaluate safety and efficacy. Given that systemic hypersensitivity reaction occurs in 0.7% of the 3000 subjects of the survey, as in the foreign clinical studies, the two-sided 95% confidence interval of the incidence is between 0.40% and 1.00%. Given that the incidences of cataract and neurocognitive disorders caused by low LDL cholesterol, which were not reported from the Japanese studies, are 1.0% and 0.8%, respectively, as in the foreign clinical studies, their 95% confidence intervals are between 0.64% and 1.36% and between 0.48% and 1.12%, respectively.

PMDA's view:

The characteristics of patients included in the clinical studies of alirocumab were not diverse, particularly in patients with hepatic impairment and elderly patients (≥75 years). Therefore, more data on safety and efficacy, the occurrence of hypersensitivity, immunogenicity, and cardiovascular events, and the effect of low LDL-C (LDL-C < 25 mg/dL) in long-term treatment with alirocumab should be collected through post-marketing surveillance or other surveys involving the patient population mentioned. Because the Japanese and foreign clinical studies did not include HoFH patients and the efficacy and safety of alirocumab in this patient population remain unknown, relevant data of these patients needs to be collected. Details of the post-marketing surveillance including the appropriateness of the safety specification, risk classification, pharmacovigilance activities, and risk minimization activities will be finalized in accordance with the Risk Management Plan Guidance (PFSB/SD Notification No. 0411-1, PFSB/ELD Notification No. 0411-2 dated April 11, 2012) and in light of comments from the Expert Discussion.

8. Results of Compliance Assessment Concerning the New Drug Application and Conclusion Reached by PMDA

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

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that alirocumab has efficacy in the treatment of HC (including FH), and that alirocumab has acceptable safety in view of its benefits. Alirocumab is of clinical significance because it offers a new treatment option for patients with HC. The indications, dosage and administration, precautionary statements in the package insert, and survey items in post-marketing investigation should be further discussed.

PMDA has concluded that alirocumab may be approved if alirocumab is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

April 25, 2016

Product Submitted for Approval

Brand Name	(a)	Praluent 75 mg Solution for Injection in Pre-filled Syringe Praluent 150 mg Solution for Injection in Pre-filled Syringe
	(b)	Praluent 75 mg Solution for Injection in Pre-filled Pen Praluent 150 mg Solution for Injection in Pre-filled Pen
Non-proprietary Name	Alirocumab (Genetical Recombination)	
Applicant	Sanofi K.K.	
Date of Application	August 06, 2015	

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized in the following. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, 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).

1.1 Clinical positioning

Japanese and foreign treatment guidelines for hypercholesterolemia (HC) mention HMG-CoA reductase inhibitors (hereinafter referred as to "statins") as the first-line drugs in drug therapy. The Japanese phase III study demonstrated the add-on effect of Praluent 75 mg or 150 mg Solution for Injection in Pre-filled Syringe and Praluent 75 mg or 150 mg Solution for Injection in Pre-filled Pen (hereinafter referred to as "the product") in reducing low-density lipoprotein-cholesterol (LDL-C) and its acceptable safety when co-administered with a statin. Therefore, PMDA has concluded that the product should be used with a conventional therapy including a statin in patients at high cardiovascular risks who do not respond adequately to a statin alone. The PMDA's conclusion was supported by the expert advisors.

1.2 Indications

PMDA has concluded that the product should be used, in light of its clinical positioning, in HC patients who do not adequately respond to conventional therapies including at least a statin, and that the product should be selected only for HC patients at high cardiovascular risks with a substantial need to reduce LDL-C. PMDA has also concluded that the additional indication of heterozygous familial hypercholesterolemia (HeFH) was justified by the results of the Japanese phase III study. Furthermore, PMDA has concluded that the package insert should indicate points to consider in the assessment of risk of cardiovascular events in HC patients (presence or absence of risk factors other than high LDL-

cholesterolemia) and appropriately disseminate the characteristics of patients included in the Japanese phase III study. All PMDA's conclusions were supported by the expert advisors.

The efficacy and safety of alirocumab have not been investigated well in patients with homozygous familial hypercholesterolemia (HoFH). However, genetic testing is not a common clinical practice, and alirocumab is expected to be effective in patients having LDLR even with the phenotype of HoFH because of its mechanism of action. PMDA therefore concluded that the product can be supplied to medical sites as a drug to be prescribed to both HeFH and HoFH patients, that alirocumab should not be continued aimlessly and rather be discontinued when the patient does not respond to its LDL-C lowering effect (e.g., *LDLR*-null HoFH patients), and that healthcare professionals should be advised to determine whether to continue the treatment based on not only the safety but also the efficacy of alirocumab. All these conclusions reached by PMDA were supported by the expert advisors.

Accordingly, PMDA concluded that the "Indications," "Precautions for Indications," and "Precautions for Dosage and Administration" sections should be modified as follows.

Indications

Familial hypercholesterolemia and hypercholesterolemia

However, the use of the product should be limited to patients at high risk of cardiovascular events with an inadequate response to HMG-CoA reductase inhibitors

Precautions for Indications

1. Before considering the use of the product, affirm the diagnosis of familial hypercholesterolemia or hypercholesterolemia by appropriate examinations and tests.
2. Before treating patients with non-familial hypercholesterolemia, confirm that the patient is at high risk of cardiovascular events based on the presence or history of coronary artery diseases, non-cardiogenic cerebral infarction, peripheral arterial diseases, diabetes mellitus, or chronic kidney diseases, to determine whether to use the product (see the "Clinical Studies" section).
3. The efficacy and safety of the product have not been established in patients with homozygous familial hypercholesterolemia. The eligibility of patients for the use of the product should be carefully assessed, and the treatment should be discontinued if the patient does not respond to the product (see the "Important Precautions" section).

Precautions for Dosage and Administration

The product should be co-administered with an HMG-CoA reductase inhibitor.

(The efficacy and safety of alirocumab monotherapy have not been established in Japanese patients.)

(The rest omitted)

1.3 Justification of the primary endpoints

The effect of alirocumab to reduce cardiovascular events has not been demonstrated in the available clinical study data. However, the LDL-C lowering effect of statins or other drugs is suggested to contribute to the suppression of cardiovascular events, and alirocumab posed no significant safety concerns in long-term use. Therefore, PMDA concluded that providing alirocumab with its proven LDL-C lowering effect to medical sites is justifiable at this point. Data should be further collected through post-marketing surveillance, etc. on the effect of alirocumab on the incidence of cardiovascular events in clinical use in Japan. Furthermore, the ODYSSEY OUTCOMES study is underway to evaluate alirocumab's capacity to prevent the recurrence of cardiovascular events. The study results should be closely observed. All PMDA's conclusions were supported by the expert advisors.

1.4 Dosage and administration

The Japanese phase III study demonstrated the efficacy of alirocumab, where the starting dose of 75 mg once every 2 weeks (Q2W) was maintained in most subjects. PMDA concluded that the usual dosage and administration of this product should be 75 mg Q2W. This PMDA's conclusion was supported by the expert advisors.

Although only 2 subjects experienced dose increase to 150 mg Q2W in the Japanese phase III study (Study EFC13672), patients having high HDL-C including those with HeFH may require dose increase to achieve the target LDL-C control value. A greater LDL-C lowering effect was observed in the 150 mg Q2W group than in the 75 mg Q2W group in the Japanese phase II study (Study DFI12361). Foreign clinical studies demonstrated an additional LDL-C lowering effect after dose increase from alirocumab 75 mg Q2W to 150 mg Q2W. Based on these results, PMDA concluded dose increase from alirocumab 75 mg Q2W to 150 mg Q2W is a therapeutic option that benefits patients. This PMDA's conclusion was supported by the expert advisors.

Accordingly, PMDA concluded that the dosage and administration should be described as follows.

Dosage and Administration

The usual adult dosage is 75 mg of alirocumab (genetical recombination) administered by subcutaneous injection once every 2 weeks. The dose may be increased to 150 mg for patients not adequately responding to 75 mg.

1.5 Safety

In the foreign clinical studies, systemic allergy-related AEs occurred more frequently in the alirocumab group than in the control group, with serious systemic allergy events including leukocytoclastic vasculitis. Therefore, PMDA concluded that the applicant's intention to add a precautionary statement on systemic allergy-related events in the "Clinically significant adverse reactions" section of the package insert is appropriate. This PMDA's conclusion was supported by the expert advisors.

Due to the concerns on hepatic impairment associated with alirocumab revealed by the Japanese clinical studies, an appropriate precautionary statement should be provided in the "Adverse Reactions" section of the package insert. Because the Japanese and foreign phase III studies excluded patients with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) of >3-fold the upper limit normal (ULN) and there is limited data on the safety of alirocumab in patients with hepatic impairment, precautionary statements that alirocumab should be administered with care to patients with severe hepatic impairment and that there is no clinical experience of alirocumab in patients with severe hepatic impairment should be included. All these conclusions reached by PMDA were supported by the expert advisors.

Besides the above-mentioned events, AEs possibly associated with the alirocumab are excessively decreased LDL-C, injection site reactions, increased creatine phosphokinase (CK), musculoskeletal AEs, antibody production, effect on cognitive function, ophthalmic effects, hormonal effects, and effects on diabetes mellitus or increased blood sugar levels. Despite the possibility that treatment with alirocumab will be continued for several decades, there are limited experiences in long-term treatment. Considering this, PMDA concluded that the long-term safety of alirocumab in relation to these events should be further investigated through post-marketing data, and that appropriate measures should be taken according to available new findings. The PMDA's conclusion was supported by the expert advisors.

Accordingly, PMDA requested the applicant to include "serious systemic allergy" in the "Clinically significant adverse reactions" section and alirocumab-associated hepatic impairment in the "Adverse reactions" section, specify patients with severe hepatic impairment in the "Careful administration" section, and collect data on the events that may potentially be caused by alirocumab and the safety of alirocumab in patients with hepatic impairment. The applicant appropriately responded to the PMDA's request.

1.6 Risk management plan (draft)

In view of the discussions presented in the Section "7.R.6 Post-marketing investigations" of Review Report (1) and comments from expert advisors at the Expert Discussion, PMDA concluded that the risk management plan (draft) for this product should include the safety and efficacy specifications shown in Table 51, additional pharmacovigilance actions and risk minimization actions shown in Table 52, and special drug use-results survey shown in Table 53.

Table 51. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Immunogenicity • Systemic hypersensitivity reaction	• Cataract • Neurocognitive events	• HoFH (including pediatric patients) • Patients with hepatic impairment • Effect of long-term use (including the effect of low LDL-C levels [<25 mg/dL]) • Chronic hepatitis C virus carrier/hepatitis patients • Elderly (≥75 years)
Efficacy specification		
• Efficacy in long-term clinical use		

Table 52. Summary of additional pharmacovigilance and risk minimization actions included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Special drug use-results survey (long-term use)	• Early post-marketing phase vigilance • Preparation of reference materials for healthcare professionals

Table 53. Outline of use-results survey (draft)

Objective	Evaluation of safety and efficacy in clinical use
Survey method	Central registration method
Population	FH or HC patients at high risk of cardiovascular events who do not adequately respond to HMG-CoA reductase inhibitors
Observation period	2 years
Planned sample size	3000 subjects as the safety analysis set
Main survey item(s)	Systemic hypersensitivity reaction, AEs related to immunogenicity

2. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

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

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment 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. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

The new drug application data (5.3.5.1-1, 5.3.5.1-5) were subjected to an on-site GCP inspection, 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. The clinical studies were conducted in compliance with GCP as a whole, and there were no obstacles to conducting its review based on the application documents submitted. The inspection revealed the following findings at some of the study sites used by the applicant. Despite no significant effect on the overall assessment of studies, it was notified to the heads of the study sites concerned for improvement.

Findings to be improved

Study sites

- Some patients who met an exclusion criterion (use of a lipid lowering drug other than atorvastatin 5 to 20 mg during the screening period) were enrolled in the study and received the study drug.

3. Overall Evaluation

Based on the above review, PMDA has concluded that the product may be approved after modifying the descriptions of "Indications and "Dosage and Administration" sections as shown below and with the following conditions of approval. Because the product contains 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 powerful drug, and the product is classified as a biological product.

Indications

Familial hypercholesterolemia and hypercholesterolemia

However, the use of the product should be limited to patients at high risk of cardiovascular events with an inadequate response to HMG-CoA reductase inhibitors

Dosage and Administration

The usual adult dosage is 75 mg of alirocumab (genetical recombination) administered by subcutaneous injection once every 2 weeks. The dose may be increased to 150 mg for patients not adequately responding to 75 mg.

Conditions of approval

The applicant is required to develop and appropriately implement a risk management plan.