Report on the Deliberation Results

June 3, 2009

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

[Brand name]	Rasilez Tablets 150 mg
[Non-proprietary name]	Aliskiren Fumarate (JAN*)
[Applicant]	Novartis Pharma K.K.
[Date of application]	February 29, 2008

[Results of deliberation]
In the meeting held on May 29, 2009, 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 product is not classified as a biological product or a specified biological product, the re-examination period is 8 years, and neither the drug substance nor the drug product is classified as a poisonous drug or a powerful drug.

**Japanese Accepted Name (modified INN)*

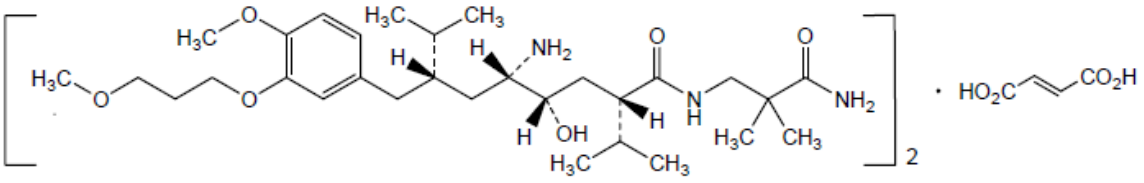
Review Report

May 21, 2009
Pharmaceuticals and Medical Devices Agency

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

[Brand name]	Rasilez Tablets 150 mg
[Non-proprietary name]	Aliskiren Fumarate
[Applicant]	Novartis Pharma K.K.
[Date of application]	February 29, 2008 (a marketing application for a drug)
[Dosage form/Strength]	A film-coated tablet containing 150 mg aliskiren
[Application classification]	Prescription drug (1) Drug with a new active ingredient

[Chemical structure]



Molecular formula: $2C_{30}H_{53}N_3O_6 \cdot C_4H_4O_4$

Molecular weight: 1219.59

Chemical name:
Bis[(2*S*,4*S*,5*S*,7*S*)-5-amino-*N*-(2-carbamoyl-2-methylpropyl)-4-hydroxy-2-1-methylethyl)-7-[4-methoxy-3-(3-methoxypropoxy)benzyl]-8- methylnonanamide]monofumarate

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

Review Results

May 21, 2009

[Brand name]	Rasilez Tablets 150 mg
[Non-proprietary name]	Aliskiren Fumarate
[Applicant]	Novartis Pharma K.K.
[Date of application]	February 29, 2008 (a marketing application for a drug)

[Results of review]
Based on the submitted data, it is concluded that the efficacy and safety of aliskiren in the treatment of hypertension have been demonstrated.

Regarding efficacy, a double-blind, comparative study was conducted to evaluate the antihypertensive effect of aliskiren 150 mg compared to placebo and losartan 50 mg in Japanese patients with essential hypertension and the primary endpoint of the absolute change from baseline in trough mean sitting diastolic blood pressure at Week 8 was significantly greater in the aliskiren group than in the placebo group and the non-inferiority of aliskiren 150 mg to losartan 50 mg was also demonstrated. Furthermore, a Japanese phase II study and a Japanese long-term treatment study suggested that aliskiren 300 mg can produce a greater blood pressure lowering effect than 150 mg. From a safety standpoint, although Japanese clinical studies raised concerns about adverse drug reactions such as hyperkalaemia and diarrhoea, it was considered that aliskiren can be started at 150 mg once daily and the dose can be increased up to 300 mg once daily. However, pharmacokinetic analyses showed that the bioavailability of aliskiren is as low as approximately 2% and that exposure variability due to the effects of food, renal function, or drug interactions may be larger than the change in the exposure after dose adjustment from 150 mg to 300 mg. Therefore, although the proposed dosage and administration (the usual dosage is 150 mg once daily and the dose may be escalated up to 300 mg) is appropriate, in view of the pharmacokinetic characteristics of aliskiren, it was considered necessary to carefully determine whether the use of aliskiren is appropriate for each patient so that aliskiren will not be administered to patients with safety concerns. Based on the above, although it is necessary to provide information regarding food effect and the patient populations to whom aliskiren should be administered with care, e.g. patients with decreased renal function and the elderly, appropriately caution about concerns regarding hyperkalaemia, diarrhoea, angioedema, etc., and collect adequate information after the market launch, it was determined that there are no serious concerns affecting the approval decision for aliskiren as long as aliskiren is used properly, including selection of eligible patients. In the course of the regulatory review, the applicant claimed that offering a choice of the 75-mg dose of aliskiren to clinical practice has little significance and withdrew the application for aliskiren 75-mg tablets.

As a result of its regulatory review, the Pharmaceuticals and Medical Devices Agency considered that the

product may be approved for the following indication and dosage and administration and concluded that the application should be deliberated by the First Committee on New Drugs.

[Indication]
Hypertension

[Dosage and administration]
Usually for adult dose, 150 mg of aliskiren is orally administered once daily. However, the dose may be escalated up to 300 mg if there is lack of efficacy.

Review Report (1)

April 24, 2009

I. Product Submitted for Registration

[Brand name] Rasilez Tablets 75 mg, Rasilez Tablets 150 mg
[Non-proprietary name] Aliskiren Fumarate
[Name of applicant] Novartis Pharma K.K.
[Date of application] February 29, 2008
[Dosage form/Strength] A film-coated tablet containing 75 mg or 150 mg aliskiren
[Proposed indication] Hypertension
[Proposed dosage and administration]
Usually for adult dose, 150 mg of aliskiren is orally administered once daily. However, the dose may be adjusted according to the patient's age and symptoms. The maximum daily dose is 300 mg.
[Items warranting special mention] None

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

The data submitted in this application and the applicant's responses to the inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below.

1. Origin or history of discovery and usage conditions in foreign countries etc.

Aliskiren is an octanamide discovered by Ciba-Geigy (a predecessor of Novartis Pharma AG, Switzerland) in 1994. Aliskiren is an oral antihypertensive agent with a novel mode of action. It selectively inhibits renin, the enzyme responsible for the first step of the renin-angiotensin system (RAS) cascade, thereby blocking the conversion of angiotensinogen to angiotensin I (Ang I). Aliskiren was approved for the indication of "hypertension" in the US in March 2007. Since then, aliskiren has been approved in 76 countries including EU member countries (as of March 2009).

In Japan, its development was initiated by Novartis Pharma K.K. in 20[redacted]. Based on the results from Japanese clinical studies etc., a marketing application for Rasilez Tablets 75 mg and 150 mg in the proposed indication of "hypertension" has now been filed.

2. Physicochemical properties and specifications

2.A. *Summary of the submitted data*

Rasilez Tablets 75 mg and 150 mg are film-coated tablets containing 82.875 and 165.750 mg, respectively, of aliskiren fumarate (with a molecular formula of $2C_{30}H_{53}N_3O_6 \cdot C_4H_4O_4$ and a molecular weight of 1219.59).

2.A.(1) Drug substance

2.A.(1).1) Characterization

(a) Structure

The drug substance is a single diastereoisomer having 4 asymmetric carbons in its chemical structure, all *S*-configurated. Its chemical structure has been elucidated by elementary analysis, mass spectrometry, ultraviolet spectroscopy, infrared spectrophotometry (IR), hydrogen nuclear magnetic resonance spectrometry (^{1}H-NMR), carbon nuclear magnetic resonance spectrometry, and X ray crystallography.

(b) General properties

The general properties of the drug substance, including description, solubility, hygroscopicity, melting point, dissociation constant (pKa), distribution coefficient, optical rotation, and crystalline polymorphism, have been determined. The drug substance is a white to slightly yellowish powder. It is freely soluble in water and in 0.1 mol/L hydrochloric acid, sparingly soluble in ethanol (99.5), and very slightly soluble in acetonitrile. It rapidly absorbs moisture when the relative humidity is above 66% and deliquescence occurs when the water content is above about 6%. Its melting point is 95°C to 104°C, pKa is 9.19, its distribution coefficient is 10.3 (1-octanol/phosphate buffer pH = 7.4), and its optical rotation is -37.0 to -41.5 (1% ethanol). The polymorphic forms of the drug substance, Form A and Form B, have been identified and the crystalline form of the drug substance is thermodynamically stable Form A containing [redacted]. Since Form A is [redacted] obtained by [redacted] of [redacted] and it is partially [redacted] through [redacted], [redacted] of the drug substance is [redacted]% to [redacted]% ([redacted] method). Form A and Form B are distinguishable by X-ray powder diffraction. Form B was not detected in the lots used during development, nor was any polymorphic transition from Form A to Form B observed in long-term or accelerated stability studies.

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

The manufacturing process for the drug substance consisted of the following 3 steps. In Step 1 (synthesis of [redacted]), [redacted], [redacted], and [redacted] were suspended and dissolved in [redacted] ([redacted]) with the aid of heat at [redacted]°C and [redacted] was evaporated. After the addition of [redacted] for cooling, the mixture was added with [redacted] solution or water and washed to [redacted] [redacted], which was then evaporated [redacted] to obtain [redacted]. The thus-obtained [redacted] was dissolved in [redacted]. In Step 2 (synthesis of aliskiren), [redacted]% or [redacted]% [redacted] was suspended in [redacted], added with [redacted] solution of [redacted], and, [redacted], agitated [redacted] at [redacted]°C to obtain aliskiren [redacted] solution. In Step 3 (synthesis of aliskiren fumarate), fumaric acid was added [redacted] or fumaric acid [redacted] solution was added to aliskiren [redacted] solution, agitated, and [redacted] at [redacted]°C or [redacted]°C until the amount of [redacted] solution accounted for [redacted]% or [redacted]% of [redacted]. Then [redacted] was added so that the ratio of [redacted] to [redacted] was [redacted] : [redacted], and the mixture was [redacted] to [redacted]°C before filtration. [redacted] of [redacted] was added into [redacted] at [redacted]°C to [redacted] aliskiren fumarate and [redacted] was added to induce [redacted]. Furthermore, [redacted] [redacted] was used to allow the ratio of [redacted] to [redacted] to be [redacted] : [redacted] and then [redacted] ([redacted]°C) and [redacted] ([redacted]°C) were [redacted]. After [redacted] cooling, a solid was filtered, washed with a

mixture of [redacted] ([redacted] : [redacted]), and dried in vacuum to obtain the drug substance. In Step 4 (milling), the drug substance was milled. In Step 5 (packaging), the drug substance was filled into [redacted] bags or [redacted] bags and placed in drums.

2.A.(1).3) Control of critical process steps

Step [redacted] has been defined as a critical process step. [redacted] at the time of [redacted] of aliskiren [redacted] solution and [redacted] of [redacted] to [redacted] in [redacted] were controlled as critical parameters.

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

Before the manufacturing process (on a commercial scale) was established, the following changes had been made: (i) In Step 1, the addition of [redacted] was omitted, (ii) In Step 2, reaction solvent was changed from [redacted] to [redacted] and the use of [redacted] was omitted, and (iii) In Step 3, [redacted] process of the drug substance was changed.

2.A.(1).5) Control of drug substance

The proposed specifications for the drug substance include appearance (visual), identification (IR and X-ray powder diffraction method), optical rotation, purity (heavy metals, related substances [liquid chromatography (HPLC), capillary electrophoresis (CE), ion exchange chromatography, [redacted] analysis], residual solvents [gas chromatography (GC)], [redacted] [[redacted] method]), water content, residue on ignition, particle size, assay (HPLC), and microbial limits.

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

As stability studies of the drug substance, testing (a) and (c) using 3 lots produced at a pilot scale, testing (e) and (f) using 1 lot produced at a pilot scale, and testing (b) and (d) using [redacted] lots produced at a commercial scale were performed.

(a) Long-term testing (25°C/60%RH, aluminum-laminated bag, 24 months)
(b) Long-term testing (25°C/60%RH, aluminum-laminated bag, 24 months)
(c) Accelerated testing (40°C/75%RH, aluminum-laminated bag, 6 months)
(d) Accelerated testing (40°C/75%RH, aluminum-laminated bag, 6 months)
(e) Stress testing (40°C/75%RH, 50°C/< 30%RH, 50°C/75%RH, 60°C/< 30%RH, 60°C/75%RH, exposed sample and sample in an aluminum-laminated bag, 1 month)
(f) Photostability testing (xenon lamp, exposed sample, 1.2 million lx·h, ≥ 200 W·h/m^2)

Samples were tested for appearance, related substances (HPLC), water content, and assay at all timepoints in (a) to (f), for appearance of solution at 0, 3, 6, 12, and 24 months in (a), at 0, 12, and 24 months in (b), and at all timepoints in (c), (d), and (f), for optical rotation at 0, 6, 12, and 24 months in (a), at 0, 6, 12, and 24 months in (b), and at all timepoints in (c) to (f), for related substances (CE) at 0, 12, and 24 months in (a), at 0, 12, and 24 months in (b), and at all timepoints in (c) to (f), for loss on drying at all timepoints in

(e) and (f), and for [redacted] content ([redacted] method) at 0 and 12 months in (a) and at all timepoints in (c).

The results of the stability studies using the lots produced at a pilot scale were as follows: there were slight increases in related substances in (a) and slight increases in related substances and increases in [redacted] content in (c). In (e), when the exposed samples were stored, related substances were increased, the drug substance deliquesced at a humidity of 75%, and related substances ([redacted], [redacted], [redacted]) were markedly increased and unknown degradation products were detected at 50°C/75%RH and 60°C/75%RH and when the samples were stored in aluminum-laminated bags, increases in related substances were observed at 60°C. In (f), increases in water content were noted. There were little changes in other attributes tested.

In the stability studies using the lots produced at a commercial scale, there were slight increases in related substances, but little changes in other attributes tested.

As shown in the above, the drug substance is sensitive to heat and humidity and when the sample was exposed to light, suspended particles were present in the sample solution for determination of optical rotation. However, because there were no significant changes up to 6 months under accelerated conditions and up to 24 months under long-term conditions, a re-test period of 30 months (24 months plus 6 months) has been proposed for the drug substance when stored in air-tight containers (light-resistant) at room temperature. The long-term stability studies (a) and (b) are ongoing and the planned lengths of the studies are 60 months.

2.A.(2) Reference standards or materials

The proposed specifications for the drug substance reference standard include appearance (visual), identification (IR, ^{1}H-NMR, X-ray powder diffraction method), optical rotation, purity (related substances [HPLC, CE, ion exchange chromatography], residual solvents [GC], [redacted] [[redacted] method]), water content, and assay (potentiometric titration method).

2.A.(3) Drug product

2.A.(3).1) Description and composition of the drug product

Rasilez 75 mg/150 mg tablet is a film-coated tablet comprising a core tablet and a coating layer. The core tablet is composed of aliskiren fumarate, microcrystalline cellulose (a diluent), crospovidone ([redacted]), povidone ([redacted]), magnesium stearate ([redacted]), and colloidal silicon dioxide ([redacted]). The coating layer is composed of [redacted], [redacted], and [redacted] (a coating agent).

2.A.(3).2) Formulation development

The development of the drug product containing aliskiren was initiated with an uncoated tablet (market formulation [MF] uncoated tablet). Then, a film-coated tablet (MF tablet) was chosen in order to mask the

bitter taste of the drug substance and the [redacted]-mg tablet core [redacted] remained unchanged while the amount of [redacted] in the tablet core was optimized for [redacted] and [redacted]-mg tablets. Furthermore, in order to change [redacted] of [redacted] that was [redacted] for the MF tablet, [redacted] and [redacted] of the coating were changed and this formulation was chosen as the final market image (FMI) tablet.

MF uncoated tablet and MF tablet were encapsulated in order to maintain the blinding for use in clinical trials. [redacted]-mg over-encapsulated MF and FMI tablets and [redacted]-mg over-encapsulated MF uncoated, MF, and FMI tablets showed similar dissolution behavior. On the other hand, although direct comparison was not made for dissolution behavior of [redacted]-mg tablets, the applicant considered that based on the dissolution behavior of [redacted] and [redacted]-mg tablets, [redacted]-mg over-encapsulated MF uncoated and FMI tablets also show similar dissolution behavior.

A bioequivalence (BE) study of 150-mg over-encapsulated MF and FMI tablets was conducted to confirm that encapsulation has no effect on bioavailability (BA). As a result, the BE criteria were not met for the maximum plasma concentration (C_{max}) while the BE criteria were met for the area under the plasma concentration-time curve (AUC_{0-t}) [see 4.(i).A.(1) Bioequivalence (BE) between different formulations].

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

The manufacturing process for the drug product consisted of the following steps. In Step 1 (blending process 1), the drug substance, [redacted], [redacted], and [redacted] were blended using [redacted] machine. In Step 2 (granulation process 1), [redacted] was dissolved in [redacted]% [redacted], which was added to the mixture obtained in Step 1 for granulation. [redacted]% [redacted] was added until [redacted] in Step 3 (granulation process 2) and kneaded to [redacted] in Step 4 (kneading process). [redacted] was sized with a sizing machine in Step 5 (sizing process 1) and dried with [redacted] dryer in Step 6 (drying process 1). In Step 7 (sizing process 2/drying process 2), the granules were sized with a sizing machine (screen size, [redacted] mm) and dried with [redacted] dryer if the action limit was not met. In Step 8 (sizing process 3) and Step 9 (sizing process 4), the sized granules obtained from their respective previous steps were sized with a sizing machine for fitting the screen sizes of [redacted] and [redacted] mm, respectively (sized granules 1). In Step 10 (sizing process 5), [redacted], [redacted], [redacted], and [redacted] were sized with a sizing machine for fitting the screen size of [redacted] mm (sized granules 2). In Step 11 (blending process 2), the sized granules 1 and 2 were blended with a blender for tableting. In Step 12 (tableting process), the mixture granules were tabletted using a tableting machine to obtain core tablets. In Step 13 (film-coating process), after [redacted], [redacted], and [redacted] were added to [redacted] to prepare coating solution, the core tablets were film-coated using a coating machine and dried. In Step 14 (packaging process), using a Press Through Pack (PTP) packaging machine, [redacted] were molded at high temperature and then the tablets were placed in there and heat-sealed with aluminum foil (PTP sheets). Furthermore, using a pillow packaging machine, PTP sheets with silica gel were packaged in a pillow bag made of aluminum-laminated films. In Step 15 (final packaging process), the packaged tablets were packed in

cartons (the product). No critical process step has been identified and the action limits have been established for Steps [redacted], [redacted], and [redacted].

2.A.(3).4) Control of drug product

The proposed specifications for the drug product include appearance (visual), identification (ultraviolet-visible spectrophotometry), purity (related substances [HPLC], [redacted] and [redacted] [GC]), water content, uniformity of dosage units (mass variation test), dissolution (dissolution test), and strength (HPLC).

2.A.(3).5) Stability of drug product

Testing (a) to (c) using 3 lots each of the 75- and 150-mg tablets and testing (d) using 1 lot each of the 75- and 300-mg tablets were conducted. Testing (d) was performed according to a bracketing design and the photostability of the 150-mg strength tablets was inferred based on the results of photostability testing of the 75- and 300-mg tablets as the core tablet compositions of all the strengths are the same.

(a) Long-term testing (25°C/60%RH, PTP sheet + silica gel/aluminum pillow package, 24 months)
(b) Accelerated testing (40°C/75%RH, PTP sheet + silica gel/aluminum pillow package, 6 months)
(c) Stress testing (50°C, PTP sheet + silica gel/aluminum pillow package, 3 months)
(d) Photostability testing (xenon lamp, the exposed drug product, 1.2 million lx·h and ≥ 200 W·h/m^2)

Samples were tested for appearance, related substances, water content, dissolution, and strength at 0, 3, 6, 9, 12, 18, and 24 months in (a), at 0, 1, 3, and 6 months in (b), and at 0, 1, and 3 months in (c). Samples were tested for appearance, related substances, and strength before and after light exposure in (d). Microbial limits test was performed at 0 and 12 months in (a).

Among the above stability studies, the stress study showed increases in related substances while all of the long-term (24 months), accelerated, and photostability studies revealed no significant changes in all attributes tested. Since the photostability study showed no changes in all attributes tested, the 150-mg tablets were also considered to be photostable. Based on these results, a shelf life of 36 months (24 months [24 months stability data under long-term conditions are available] plus 12 months) has been proposed for the drug product when stored in a PTP sheet packed in an aluminum pillow bag containing silica gel at room temperature. The long-term stability study is ongoing and the planned length of the study is 36 months.

2.B. *Outline of the review of PMDA*

2.B.(1) Drug product specifications

PMDA asked the applicant to provide a justification for the Q value [redacted]% in dissolution testing, based on the measured values and by showing the expected failure rate if the Q value is set at [redacted]%.

The applicant responded as follows:

According to the results of dissolution testing of the 75- and 150-mg tablets, the mean minimum value was

[redacted]% (ranging from [redacted]% to [redacted]%) and [redacted]% (ranging from [redacted]% to [redacted]%), respectively, and the lower limit of the mean minimum value ± 3σ was [redacted]% and [redacted]%, respectively. If the Q value is set at [redacted]%, the tablets may fail the dissolution test at the level of [redacted], but are unlikely to fail the test at the level of [redacted]. Thus, the dissolution specification will be changed to "Q = [redacted]% in [redacted] minutes."

PMDA accepted the applicant's response.

2.B.(2) Stability of drug product

While the stability of the drug product was studied when kept in a PTP sheet packaged in an aluminum pillow bag containing silica gel, it is envisaged that the drug product packaged in a PTP sheet only may be stored in clinical practice. PMDA asked the applicant to explain the stability of the drug product packaged in a PTP sheet only.

The applicant responded as follows:

The stability of the drug product packaged in a PTP sheet after opening the aluminum pillow bag was studied using 1 lot each of the 75- and 150-mg tablets produced at a commercial scale when stored for 6 months under long-term (25°C/60%RH) and intermediate (30°C/75%RH) conditions. As a result, there were no changes from baseline in all attributes tested and the drug product was stable under the long-term conditions while increases in water content were only observed under the intermediate conditions. In addition, 3 lots of the 75-mg tablets produced at a pilot scale and at a commercial scale were stored for 24 months under long-term conditions (25°C/60%RH) and for 9 months under intermediate conditions (30°C/65%RH). As a result, increases in water content were only observed. As shown in the above, the drug product packaged in a PTP sheet after opening the aluminum pillow bag was stable up to 6 months under the long-term conditions (25°C/60%RH), whereas there were increases in water content, exceeding the specification limit (≤ [redacted]%) at 3 months (30°C/75%RH) and at 6 months (30°C/65%RH) under the intermediate conditions. Taking account of these findings, it is cautioned in the storage section of the proposed package insert that "Store protected from moisture after opening the aluminum pillow bag" and in the expiration date section that "Use as soon as possible after opening the aluminum bag even before the expiration date."

PMDA accepted the applicant's response.

Based on the above, PMDA concluded that there are no particular problems with the quality of aliskiren.

3. Non-clinical data

3.(i) Summary of pharmacology studies

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

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

Among the submitted data, the results from studies related to blood pressure are as follows.

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

(a) Inhibitory potency and specificity for renin (Attached document 4.2.1.1-1, -12)

The potency of aliskiren to inhibit the enzymatic activity of human recombinant renin, human cathepsin D, human cathepsin E, human pepsin, and HIV-1 protease was evaluated based on their cleavage activities toward their respective substrates. The 50% inhibitory concentrations (IC_{50}) of aliskiren against human renin and human cathepsin D were 0.6 and 5000 nM, respectively, and the IC_{50} values of aliskiren against human cathepsin E, human pepsin, and HIV-1 protease were all ≥ 10 000 nM.

(b) Potency to inhibit human and animal renin (Attached document 4.2.1.1-1, -12, -16)

The potency of aliskiren to inhibit the activity of endogenous renin in the plasma from different animal species was evaluated based on the angiotensinogen-cleaving activity in the plasma from different animal species. The IC_{50} values of aliskiren against endogenous renin in the plasma from human, marmoset, mouse, rat, dog, rabbit, cat, pig, and guinea pig were 0.6, 2, 4.5, 80, 7, 11, 8500, 150, and 63 nM, respectively.

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

3.(i).A.(1).2).(a) Antihypertensive effects of aliskiren in SD rats overexpressing human renin and angiotensinogen genes (double transgenic rats [dTGR])

i) Antihypertensive effects and effects on heart rate following a single oral dose of aliskiren (telemetry) (Attached document 4.2.1.1-2)

Male dTGR (8-12 weeks of age, n = 8) received a single oral dose of aliskiren at doses of 0.3, 1, 3, 10, 30, or 100 mg/kg or vehicle and mean arterial pressure (MAP) and heart rate were measured in conscious, freely moving rats by telemetry. Aliskiren induced almost dose-dependent reduction in MAP and the maximum change in MAP (peak response) from baseline (the mean of all MAP values obtained every 10 minutes over at least 1 day prior to the dosing of the test agent) following dosing of aliskiren was -13 ± 6 (mean ± standard error [SE]), -19 ± 4, -28 ± 7, -45 ± 5, -60 ± 6, and -74 ± 6 mmHg, respectively, at doses of 0.3, 1, 3, 10, 30, and 100 mg/kg. In the 100 mg/kg group, MAP reduction lasted for more than 24 hours after dosing and the area under the heart rate-time curve from 0 to 6 hours was significantly higher than in the vehicle group. On the other hand, a significant increase in heart rate was noted in animals receiving aliskiren at ≥ 30 mg/kg.

ii) Antihypertensive effects following a single intravenous dose of aliskiren (catheterization) (Attached document 4.2.1.1-3)

Male dTGR (11 weeks of age, n = 3) received a single intravenous dose of 2 mg/kg of aliskiren and conscious MAP was measured via the chronically catheterized femoral artery and the change from baseline in MAP (ΔMAP) was calculated. MAP decreased by 19 ± 12 mmHg from baseline at 5 minutes post-dosing and reached maximum at 2 hours post-dosing (MAP, 84 ± 10 mmHg; ΔMAP, -86 ± 9 mmHg).

MAP and ΔMAP were sustained at ≤ 100 mmHg and at ≤ -70 mmHg, respectively, for 8 hours and returned to baseline by 48 hours post-dosing.

iii) Antihypertensive effects following a single oral dose of aliskiren (catheterization) (Attached document 4.2.1.1-3)

Male dTGR (11 weeks of age, n = 3) received a single oral dose of 3, 10, or 30 mg/kg of aliskiren. Conscious MAP was measured via the chronically catheterized femoral artery. Following aliskiren dosing, MAP began to decrease at 15 minutes (10 and 30 mg/kg) or at 30 minutes (3 mg/kg) and the peak effect was reached at 1 hour post-dosing in the 3 mg/kg group and at 8 hours post-dosing in the 10 and 30 mg/kg groups, and then MAP returned to baseline by 48 hours post-dosing. The absolute maximum change in MAP following an oral dose of 30 mg/kg (70 ± 14 mmHg) was smaller than the absolute maximum change in MAP following an intravenous dose of 2 mg/kg (86 ± 9 mmHg).

iv) Antihypertensive effects following repeated oral doses of aliskiren (telemetry) (Attached document 4.2.1.1-2)

Male dTGR (8-12 weeks of age, n = 5) orally received aliskiren (1, 3, or 10 mg/kg) or vehicle once daily for 10 days and MAP and heart rate were measured in conscious, freely moving rats by telemetry. Aliskiren induced a dose-dependent reduction in MAP and there was no evidence for attenuation or potentiation of the antihypertensive effect over time throughout the dosing period of 10 days at all dose levels of aliskiren. Heart rate changed with MAP changes at all dose levels of aliskiren and a significant increase in heart rate (the area under the time curve from 0 to 6 hours) occurred at 10 mg/kg on Days 1 and 10 compared to the vehicle group.

v) Potency comparison with valsartan and enalapril (catheterization) (Attached document 4.2.1.1-4)

Male dTGR (5 weeks of age, n = 3-5) intravenously received aliskiren (cumulative administration of 0.01→0.03→0.1→0.3→1→3 mg/kg as aliskiren), valsartan (0.003→0.01→0.03→0.1→0.3→1 mg/kg), and enalapril (0.003→0.01→0.03→0.1→0.3→1 mg/kg) or orally received aliskiren (0.3→3→30 mg/kg as aliskiren), valsartan (0.1→1→10 mg/kg), and enalapril (0.01→0.1→1 mg/kg). MAP before the administration of the test agent and steady-state MAP after each incremental dose were measured via the chronically catheterized femoral artery and ΔMAP at each cumulative dose was calculated. Regarding the cumulative dose-ΔMAP relationship (the dose-ΔMAP curve) for each drug, these three agents, given intravenously, exhibited almost comparable dose-ΔMAP profiles while the dose-ΔMAP curve of orally administered aliskiren was shifted to the right compared to those of orally administered valsartan and enalapril.

3.(i).A.(1).2).(b) Pharmacokinetic/pharmacodynamic evaluation and antihypertensive effects in dTGR

i) Relationship between the area under the ΔMAP or change in heart rate (ΔHR)-time curve and the dose (Attached document 4.2.1.1-3)

Male dTGR (11 weeks of age, n = 3) received a single oral dose of 3, 10, or 30 mg/kg of aliskiren and conscious MAP and heart rate were measured via the chronically catheterized femoral artery. Based on ΔMAP and ΔHR, the areas under the ΔMAP or ΔHR-time curve from baseline to peak response, 8, 24, and 48 hours were calculated and plotted against the dose. Aliskiren dose-dependently reduced MAP and ΔMAP was decreased over time from peak response to 8, 24, and 48 hours. ΔHR tended to increase with increasing dose, but was not dose-dependent.

ii) Correlation between dose and exposure and between exposure and antihypertensive effects (Attached document 4.2.1.1-3)

Male dTGR (11 weeks of age, n = 3) received a single oral dose of 3, 10, or 30 mg/kg of aliskiren and conscious MAP was measured via the chronically catheterized femoral artery. The areas under the ΔMAP-time curve and AUCs of plasma aliskiren from baseline to peak response, 8, 24, and 48 hours were calculated, which suggested that the AUC correlates with the dose of aliskiren and the AUC correlates with the area under the ΔMAP-time curve.

3.(i).A.(1).2).(c) Antihypertensive effects in marmosets

i) Single oral dose study in severely sodium (Na)-depleted marmosets (Attached document 4.2.1.1-5, -15)

Marmosets were maintained on a low-Na diet for 1 week before drug treatment and during the experiment. All animals received furosemide in drinking water (6 mg/kg/day) 2 days before the start and an intramuscular dose (9 mg/kg) 20 hours before drug treatment (severely Na-depleted marmosets) (males, 350 g, n = 5-11). A single oral dose of 0.3, 1, 3, or 10 mg/kg of aliskiren or vehicle was administered to the severely Na-depleted marmosets and MAP and heart rate were measured by telemetry in conscious, unrestrained animals. Aliskiren caused dose-dependent reductions in MAP and the duration of MAP reduction ≥ 20 mmHg at 3 and 10 mg/kg was about 5 and 16 hours, respectively. On the other hand, aliskiren had no significant effect on heart rate at any dose level.

ii) Repeated oral dose study in mildly Na-depleted marmosets (Attached document 4.2.1.1-6, -12)

Marmosets maintained on a low-Na diet for 1 week before drug treatment and during the experiment (mildly Na-depleted marmosets) (males, 350 g, n = 4-10) received 3 or 10 mg/kg of aliskiren or vehicle orally once daily for 8 days. MAP and heart rate were measured by telemetry in conscious, unrestrained animals. At a dose of 3 mg/kg, aliskiren lowered MAP by approximately 10 mmHg within 2 hours of administration on the first day of dosing and MAP remained lowered during repeated dosing. The dose of 10 mg/kg lowered MAP by approximately 13 mmHg within 2 hours of administration on the first day of dosing and MAP remained lowered during repeated dosing, but tended to rise after the end of treatment with aliskiren. No significant changes from baseline in heart rate were seen in any group.

3.(i).A.(1).2).(d) RAS inhibition in marmosets

i) Plasma concentrations of aliskiren and plasma renin activity (PRA) in severely Na-depleted marmosets (Attached document 4.2.1.1-5, -15)

Severely Na-depleted marmosets (females, 350 g, n = 3-4) received a single oral dose of 0.3, 1, 3, or 10 mg/kg of aliskiren or vehicle or a single intravenous dose of 0.003, 0.01, 0.03, or 0.1 mg/kg of aliskiren or vehicle. Femoral venous blood was sampled at pre-dose and 1.5, 3, 6, and 24 hours post-dose and plasma concentrations of aliskiren were measured using an enzymatic assay and PRA was measured by the antibody trapping method. PRA inhibition (%) was calculated as follows: (1 − PRA at each timepoint of measurement/pre-dose PRA) × 100.

PRA was inhibited by 99%, 87%, and -23%, respectively, at 3, 6, and 24 hours after the oral dose of 0.3 mg/kg and PRA was inhibited by 100% up to 24 hours after oral administration of 3 and 10 mg/kg. On the other hand, after the intravenous administration of 0.003 mg/kg, PRA was inhibited by 91% and 75%, respectively, at 1.5 and 3 hours and was inhibited by 41% at 6 hours. PRA was inhibited by 99%, 92%, 67%, and 31%, respectively, at 1.5, 3, 6, and 24 hours after the intravenous dose of 0.01 mg/kg. PRA was inhibited by 100%, 100%, 100%, and 61%, respectively, at 1.5, 3, 6, and 24 hours after the intravenous dose of 0.1 mg/kg. Plasma concentrations of aliskiren increased dose-dependently up to 3 hours after both oral and intravenous administration, but decreased over time thereafter in all groups.

ii) Effects on Plasma Active Renin Concentration (PARC) and Plasma Total Renin Concentration (PTRC) in mildly Na-depleted marmosets (Attached document 4.2.1.1-6, -12)

Mildly Na-depleted marmosets (males and females, 350 g, n = 5-10) received 3 or 10 mg/kg of aliskiren or vehicle orally once daily for 8 days. PARC, PTRC, and plasma concentrations of aliskiren were measured before administration of the first dose and at 2 and 24 hours after the last dose. PARC and PTRC before treatment were similar in all treatment groups. Plasma concentrations of aliskiren at 2 and 24 hours after the last dose were 1.5 ± 0.6 and 0.07 ± 0.06 μmol/L, respectively, at 3 mg/kg and 10.7 ± 0.7 and 0.5 ± 0.5 μmol/L, respectively, at 10 mg/kg. PARC and PTRC both dose-dependently increased at 2 and 24 hours after the last dose of aliskiren and PARC and PTRC were higher in the aliskiren groups than in the vehicle group even at 24 hours after the last dose. In the vehicle group, PARC and PTRC remained almost unchanged at all timepoints.

3.(i).A.(1).2).(e) Antihypertensive effects in Spontaneously Hypertensive Rat (SHR)

i) Continuous subcutaneous infusion study (telemetry) (Attached document 4.2.1.1-15)

Male SHR (20-30 weeks of age, n = 8-9) received continuous subcutaneous infusion of aliskiren (10, 30, or 100 mg/kg/day) or vehicle for 2 weeks and MAP was measured by telemetry in conscious, unrestrained animals. MAP reductions were sustained throughout the dosing period in the aliskiren 30 and 100 mg/kg/day groups while MAP beyond Treatment Week 1 in the 10 mg/kg/day group was similar to that in the vehicle group. The reduced MAP in the aliskiren 30 and 100 mg/kg/day groups rose slowly after the end of treatment.

3.(i).A.(1).2).(f) Study in other disease models

i) Antihypertensive effects and PRA inhibition in renin-dependent, renovascular and volume overload hypertension models in mice (Attached document 4.2.1.1-7)

2K1C mice (ApoE knockout C57/BL/6 mice [ApoE$^{-/-}$mice] subjected to clipping of the left renal artery) (a renin-dependent, renovascular hypertension model) (males and females, 15-16 weeks of age, n = 6-9), 1K1C mice (ApoE$^{-/-}$ mice subjected to uninephrectomy and clipping of the remaining renal artery) (a volume overload hypertension model) (males and females, 15-16 weeks of age, n = 7-10), and ApoE$^{-/-}$mice subjected to the sham procedure (males and females, 15-16 weeks of age, n = 6-7) were subcutaneously treated with 50 mg/kg/day of aliskiren or vehicle for 4 weeks, starting 1 week after surgery, and MAP and heart rate were measured via the chronically catheterized carotid artery of conscious animals at the end of treatment with the test agent. PRA at the end of treatment was calculated based on the generated Ang I measured by the antibody trapping method. In sham mice, aliskiren lowered MAP to 91 ± 1.9 mmHg, which was significantly lower than 114 ± 2.5 mmHg in sham vehicle controls. MAP in vehicle-treated 2K1C and 1K1C mice were 149 ± 1.1 and 151 ± 1.0 mmHg, respectively, which were both significantly higher than MAP in vehicle-treated sham mice. MAP in aliskiren-treated 2K1C mice was 102 ± 2.3 mmHg, which was significantly lower than in vehicle-treated 2K1C mice. MAP in aliskiren-treated 1K1C mice was 117 ± 1.7 mmHg, which was significantly lower than that in vehicle-treated 1K1C mice. Aliskiren had no significant effect on heart rate in both hypertension models.

PRA in vehicle-treated 2K1C mice was 9.9 ng/mL/h, which was not significantly different from PRA (5.7 ng/mL/h) in sham vehicle mice. PRA in aliskiren-treated 2K1C mice was 0.6 ± 0.1 ng/mL/h, which was significantly lower than that in vehicle controls (aliskiren inhibited PRA by 94% relative to vehicle control). There were no significant differences in PRA between vehicle-treated 1K1C and sham mice. Although aliskiren inhibited PRA in 1K1C mice by 58% relative to vehicle-treated 1K1C mice and by 68% in sham mice vs. sham vehicle-treated mice, these differences were not statistically significant.

3.(i).A.(2) Secondary pharmacodynamics

No data submitted.

3.(i).A.(3) Safety pharmacology

3.(i).A.(3).1) Interactions of aliskiren with neurotransmitter receptors (*in vitro*) (Attached document 4.2.1.3-1)

Aliskiren was evaluated for its interactions with 16 different neurotransmitter receptors based on the inhibitory effect of aliskiren 10 µM on the binding of ^{3}H-labeled ligands at their respective neurotransmitter receptor sites. Aliskiren at a concentration of 10 µM inhibited ^{3}H-labeled ligand binding at 5-HT$_1$ and 5-HT$_3$ serotonergic receptors, H$_1$ histaminergic receptors, µ-opioid receptors, benzodiazepine receptors, adenosine A$_1$ receptors, the glycine binding site of the N-methyl-D-aspartate (NMDA) receptor, and the MK-801 channel binding site of the NMDA receptor by 13%, 23%, 33%, 22%, 17%, 18%, 27%, and 13%, respectively. Aliskiren did not inhibit ^{3}H-labeled ligand binding at the following receptors: α_1, α_2,

or β-adrenergic receptors, 5-HT_2 serotonergic receptors, muscarinic acetylcholine M receptors, and AMPA, kainate, and NMDA glutamatergic receptors.

3.(i).A.(3).2 Effects of aliskiren on the central nervous system (*in vivo*) (Attached document 4.2.1.3-2)

Male Tif: MAGf mice (22-28 g, n = 4-20) received a single intravenous dose of 0.3, 1, 3, 6, or 10 mg/kg of aliskiren or vehicle. Male Tif: RAIf rats (110-155 g, n = 8-9) received a single intravenous dose of 0.3, 1, or 3 mg/kg of aliskiren or vehicle. Aliskiren was evaluated for its effects on the central nervous system. As a result, there were no effects on global behavior, ethanol-induced sleeping time, or passive avoidance in mice, nor on the motor coordination, horizontal and vertical locomotor activity, or body temperature in rats.

3.(i).A.(3).3 Effects of aliskiren on the renal and respiratory systems (*in vivo*) (Attached document 4.2.1.3-3)

Wistar rats (8 weeks of age) received a single intravenous doses of 0.3, 1, or 3 mg/kg of aliskiren and the effects of aliskiren on the renal (females, n = 6) and respiratory (males, n = 4) systems were investigated. As a result, there were no effects on Cl^-, Na^+, and K^+ excretion, the volume of urine, respiratory rate, tidal volume, or minute volume.

3.(i).A.(3).4 Effects of aliskiren on the cardiovascular system (*in vitro*, *in vivo*) (Attached document 4.2.1.3-3, -4, -5)

Male Wistar rats (8 weeks of age, n = 4) were intravenously administered aliskiren (0.3, 1, 3 mg/kg) and the effects of aliskiren on the cardiovascular system were investigated. Aliskiren produced a dose-dependent, transient decrease in systolic and diastolic blood pressures, but had no effect on the ECG.

In the isolated atria from guinea pigs, aliskiren (1, 3, 10 μM) had no effect on the rate or force of contraction. In the isolated rabbit heart, aliskiren (1, 3, 10, 30, 100 μM) had no effect on the following parameters: action potential duration, triangulation, reverse rate-dependency, instability, proarrhythmic potential, coronary perfusion rate, and interventricular conduction. In HEK293 cells expressing hERG channels, aliskiren (10, 100, 1000 μM) produced dose-dependent inhibition of hERG current (the rapidly activating component of the delayed rectifier potassium current [IKr]), but no effect was seen at 10 μM and 50% inhibition was not achieved even at 1000 μM. Based on the above, the applicant explained that aliskiren has little direct effect on the atrium or hERG channels in humans within the proposed dose range.

3.(i).A.(4) Pharmacodynamic drug interactions (Attached document 4.2.1.1-15)

Male SHR (20-30 weeks of age, n = 6-8) were subcutaneously treated with aliskiren 30 mg/kg/day, valsartan 1 mg/kg/day, or benazepril 1 mg/kg/day alone or aliskiren 30 mg/kg/day in combination with valsartan 1 mg/kg/day, or aliskiren 30 mg/kg/day in combination with benazepril 1 mg/kg/day, for 2 weeks and MAP and heart rate were measured by telemetry from the start of treatment through 1 week after the end of treatment. Aliskiren in combination with either valsartan or benazepril potentiated the

antihypertensive effects of these agents and MAP was reduced maximally on Day 5. Those MAP reductions were almost sustained throughout the dosing period. Increases in heart rate indicative of reflex tachycardia were seen in the aliskiren plus valsartan group and in the aliskiren plus benazepril group.

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

When single oral doses of 0.3 to 10 mg/kg of aliskiren were administered to severely Na-depleted marmosets, the percent inhibition of PRA was high regardless of dose up to 6 hours after dosing while MAP decreased dose-dependently. PMDA asked the applicant to explain the relationship between the percent inhibition of PRA by aliskiren and its antihypertensive effects.

The applicant responded as follows:

In this study, the percent inhibition of PRA was calculated based on PRA in each plasma sample measured by quantitation of generated Ang I per unit time, whereas it has been indicated that dissociation of a renin inhibitor (e.g. aliskiren) from plasma proteins during the assay may affect PRA measurement *in vitro*, depending on the experimental condition (Derkx FH et al. *Am J Hypertens.* 1991;4(7 Pt 1):602-9, Luther RR et al. *Clin Nephrol.* 1991;36:181-6, de Gasparo M et al. *Br J Clin Pharmacol.* 1989;27:587-96). While the antibody trapping method used in this study is considered appropriate as a PRA assay (Jeunemaître X et al. *Am J Hypertens.* 1989;2(11 Pt 1):819-27), it cannot be denied that *in vivo* renin activity inhibition may be overestimated due to the greater dissociation of a renin inhibitor from plasma proteins caused by various factors. The above suggests that in the presence of aliskiren, a potent renin inhibitor, even with a slight change in the concentration of unbound aliskiren in the reaction solution, Ang I cannot be quantitated accurately, which may have affected the percent inhibition of PRA. A dissociation of the correlation between the percent inhibition of PRA measured *in vitro* and the blood pressure lowering effect has been reported also with other renin inhibitors (Derkx FH et al. *Am J Hypertens.* 1991;4(7 Pt 1):602-9, Panek RL et al. *Clin Exp Hypertens A.* 1991;13:1395-414, Palmer RK et al. *Clin Exp Hypertens.* 1993;15: 663-81).

PMDA considers as follows:

Considering that the relationship between the antihypertensive effect and the percent inhibition of PRA is undefined, strictly speaking, it has not been proven that the mode of action of aliskiren is renin inhibition only. However, based on renin's physiological effects, PRA inhibition by aliskiren and its selectivity, and a dose-dependent antihypertensive effect of aliskiren in commonly used model animals etc., it can be assumed that the mode of action of aliskiren is PRA inhibition. Furthermore, the antihypertensive effects relative to a control drug etc. have suggested that aliskiren may be useful as an antihypertensive agent also in humans. Regarding the organ protective effects of aliskiren, the results from studies investigating the effects of aliskiren on Ang II concentration in renal tissue, albuminuria, left ventricular hypertrophy, diastolic cardiac dysfunction, etc. were submitted in this application. However, because the clinical significance of the results from these studies is unclear, as is the case with other similar drugs on the market, it cannot be concluded at present that aliskiren is expected to have such organ protective effects.

3.(ii) Summary of pharmacokinetic studies

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

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

3.(ii).A.(1).1) Single administration (Attached document 4.2.2.2-2, -4, 4.2.2.3-5, -6, 4.2.2.4-1)

Following single oral doses of 500, 100, 3, and 200 mg/kg of ^{14}C- or ^{3}H-aliskiren to male mice, male rats, male marmosets, and female rabbits, respectively, aliskiren was rapidly absorbed in all animal species and the plasma radioactivity or unchanged aliskiren concentration reached the C_{max} at 0.5 to 2 hours post-dosing. Based on the sum of urinary and biliary excretion following the administration of ^{3}H-aliskiren 100 mg/kg to male rats, oral absorption was estimated to be about 15% of the dose. Based on the total urinary radioactivity and fecal metabolites following the administration of ^{14}C-aliskiren 3 mg/kg to male marmosets, oral absorption was estimated to be about 25% of the dose.

On the other hand, following single intravenous doses of 10, 10, and 1 mg/kg of ^{14}C-aliskiren to male mice, male rats, and male marmosets, respectively, the plasma clearance was 2.0, 1.2, and 0.036 L/h/kg, respectively, and the steady-state distribution volume was 1.05, 7.8, and 0.58 L/kg, respectively. The elimination half-life ($t_{1/2}$) was 23.1 hours in rats and 29.2 hours in marmosets. In mice, after intravenous administration, the concentrations declined rapidly to below the quantitation limit and $t_{1/2}$ could not be evaluated. The absolute bioavailability (BA) was 1.5% in mice at 500 mg/kg, 2.4% in rats at 100 mg/kg, and 3% in marmosets at 3 mg/kg.

3.(ii).A.(1).2) Repeated administration (Attached document 4.2.2.2-1, 4.2.2.3-1, 4.2.3.2-8, -9, -10, -14, -19)

When ^{14}C-aliskiren 100 mg/kg/day was orally administered for 10 days to male rats, the accumulation ratio of the unchanged drug in plasma was 0.6 to 1.3 and no apparent increase was found after repeated administration compared to single-dose administration. When oral repeated doses of 10, 50, and 100 mg/kg/day of aliskiren were administered for 14 days to male and female marmosets, the mean C_{max} was 3.96→5.77 μg/mL (Day 1→Day 14) in males and 3.96→6.73 μg/mL in females, 6.29→12.3 μg/mL in males and 8.83→10.1 μg/mL in females, and 7.20→9.67 μg/mL in males and 7.94→10.6 μg/mL in females, respectively, and the mean $AUC_{0\text{-}24}$ was 22.0→33.9 μg·h/mL in males and 21.3→29.0 μg·h/mL in females, 58.1→107 μg·h/mL in males and 56.2→109 μg·h/mL in females, and 76.4→109 μg·h/mL in males and 84.0→142 μg·h/mL in females, respectively, and there were slight increases after 14-day repeated administration compared to single-dose administration.

When male and female rats orally received aliskiren at doses of 100, 300, and 1000 mg/kg/day for 14 days or at doses of 66, 221, and 663 mg/kg/day for 15 days, the C_{max} and AUC values on Day 14 or Day 15 were largely higher than those on Day 1, but there was no accumulation that exceeds the steady-state level predicted from single-dose administration. There were no apparent gender differences in the exposure of aliskiren. When male and female rats orally received aliskiren (50, 150, 250 mg/kg/day) for 26 weeks or male and female marmosets orally received aliskiren (2, 5, 20 mg/kg/day) for 39 weeks, the C_{max} and AUC were increased in a dose-proportional manner at lower doses (rats, 50 and 150 mg/kg/day; marmosets, 2

and 5 mg/kg/day) while more than dose-proportional increases were observed at high doses (rats, 250 mg/kg/day; marmosets, 20 mg/kg/day).

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

3.(ii).A.(2).1) Organ and tissue distribution (Attached document 4.2.2.3-1, -2)

Following a single intravenous dose of 10 mg/kg of ^{14}C-aliskiren to male pigmented rats (Lister-Hooded), radioactivity was extensively distributed throughout the body and peak concentrations of radioactivity were noted in the majority of organs and tissues at 5 minutes or 2 hours post-dose and concentrations were below the limit of quantitation ([redacted] or [redacted] μg Eq/g in plasma, [redacted] μg Eq/g in other tissues) at 14 days after dosing except for the choroid plexus, uvea, brown fat, and pituitary gland. Tissue radioactivity (per g of tissue) was highest in the kidney medulla, followed in descending order by the kidney cortex, liver, plasma, pancreas, salivary glands, and choroid plexus. Aliskiren or its metabolites showed an affinity for melanin-containing tissues and its binding was reversible. Following a single oral dose of 100 mg/kg of ^{14}C-aliskiren to male pigmented rats (Lister-Hooded), a high level of radioactivity was found mainly in the gastrointestinal mucosa and at 1 day after dosing, the radioactivity was below the limit of quantitation ([redacted] μg Eq/g in plasma, [redacted] μg Eq/g in other tissues) in all tissues except in the cecum mucosa and large intestine mucosa. When 100 mg/kg/day of ^{14}C-aliskiren was orally administered once daily for 1, 3, 7, or 10 days to male albino rats, radioactivity was eliminated within 24 hours from all tissues, except the intestinal wall, hair, and brown fat and was not taken up into the brain, irrespective of treatment duration. There was no accumulation of radioactivity in the organs and tissues following repeated administration.

3.(ii).A.(2).2) *In vitro* plasma protein binding and distribution in blood cells (Attached document 4.2.2.3-3)

Using plasma and blood from male mice, male rats, male and female marmosets, and male rabbits, the *in vitro* plasma protein binding and distribution in blood cells of ^{14}C-aliskiren were investigated. Within the concentration range of 10 to 10 000 ng/mL of aliskiren, there was no trend towards a concentration-dependent increase or decrease in the plasma unbound fraction in the mouse, rat, marmoset, or rabbit and the mean plasma unbound fraction (all concentrations) was 29%, 38%, 8%, and 43%, respectively, but the unbound fraction slightly increased at high concentrations (≥ 5000 ng/mL) in the mouse and marmoset. As to the blood/plasma distribution within the concentration range of 10 to 10 000 ng/mL of aliskiren, the mean fraction in plasma (all concentrations) was 65% in the mouse, 54% in the rat, 59% in the marmoset, and 84% in the rabbit, indicating that ^{14}C-aliskiren distributed into the blood cells, although the largest fraction was found in plasma in all species. *In vitro* distribution in blood cells was not concentration-dependent in the rat and rabbit. On the other hand, the fraction in plasma decreased at high concentrations in the mouse and marmoset.

3.(ii).A.(2).3) Placental transfer (Attached document 4.2.2.3-4, -5)

Following a single oral dose of 200 mg/kg of ^{14}C-aliskiren to rabbits on gestation day 17, the fetal concentration of radioactivity at 24 hours post-dose was 0.67 nmol/g (mean), indicating that the fetuses were exposed to aliskiren or its metabolites. Following a single oral dose of 250 mg/kg of ^{14}C-aliskiren to

rats on gestation day 13, the placental and fetal exposures were 1.2- to 2.4-fold and 0.2- to 1.8-fold, respectively, higher than the maternal blood concentration.

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

3.(ii).A.(3).1) *In vitro* metabolism of aliskiren (Attached document 4.2.2.4-3)

Liver microsomes from male rats and male marmosets were added with ^{3}H-aliskiren (1.0, 10, 100 μmol/L) and incubated in the presence of NADPH generating system. At 60 minutes, 17.6%, 25.2%, and 52.4%, respectively, of aliskiren remained unchanged in the rat liver microsomes and 5.4%, 1.7%, and 24.2%, respectively, of aliskiren remained unchanged in the marmoset liver microsomes. Five different metabolites, M1, M2, M3, M4, and M8 were identified.

3.(ii).A.(3).2) Metabolites in plasma (Attached document 4.2.2.2-2, -4, 4.2.2.3-6, 4.2.2.4-4)

After oral administration of ^{14}C-aliskiren 500, 100, 200, and 3 mg/kg to male mice, male rats, pregnant rabbits, and male marmosets, respectively, the unchanged parent compound was the major circulating component in plasma in all species, accounting for 56%, 51%, 29%, and 91%, respectively, of the AUC of total radioactivity. The major metabolites were M2, M3, M4, M5 or M6 (glucuronide conjugates of M1 and M4), and M10 or M11 in mice and rats and M2, M5 or M6, and M10 or M11 in rabbits. On the other hand, when 10 mg/kg of ^{14}C-aliskiren was intravenously administered to male mice and male rats, the unchanged parent compound accounted for 94% and 93%, respectively, of the AUC of total radioactivity.

3.(ii).A.(3).3) Metabolites in bile (Attached document 4.2.2.2-3, 4.2.2.4-1)

After intravenous administration of 10 mg/kg of ^{14}C-aliskiren to bile duct-cannulated male rats, the unchanged parent compound accounted for 64.3% of the radioactivity recovered in the bile up to 24 hours post-dose and the detected metabolites were M1, M2, M3, M4, and M5 or M6.

After oral administration of 100 mg/kg of ^{3}H-aliskiren to bile duct-cannulated male rats, the radioactivity recovered in the bile up to 72 hours post-dose accounted for 9.0% to 21.4% of the administered dose and the detected metabolites were M1 or M3, M2, and M5 or M6.

3.(ii).A.(3).4) Metabolites in feces (Attached document 4.2.2.2-2, -4, 4.2.2.3-6)

After oral administration of ^{14}C-aliskiren 500, 100, and 3 mg/kg to male mice, male rats, and male marmosets, respectively, the unchanged parent compound excreted in feces accounted for 69%, 72%, and 78%, respectively, of the administered radioactivity. The detected metabolites were M2 in mice, M1, M2, M3, M4, and M10 or M11 in rats, and M2, M3, M4, M10 or M11, and M13 or M14 in marmosets.

3.(ii).A.(3).5) Metabolites in urine (Attached document 4.2.2.2-2, -4, 4.2.2.3-6, 4.2.2.4-4)

After oral administration of ^{14}C-aliskiren 500, 100, 200, and 3 mg/kg to male mice, male rats, pregnant rabbits, and male marmosets, respectively, urinary excretion was minor in all animal species and trace amounts of metabolites were detected.

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

3.(ii).A.(4).1) Urinary and fecal excretion (Attached document 4.2.2.2-2, -4, 4.2.2.3-1, 4.2.2.3-6)

After ^{14}C-aliskiren 10, 10, and 1 mg/kg were intravenously administered to male mice, male rats, and male marmosets, respectively, the fecal excretion of radioactivity up to 72, 96, and 168 hours post-dose was 91%, 90%, and 72% of the dose, respectively and the urinary excretion of radioactivity was 2%, 4%, and 4% of the dose, respectively. After oral administration of ^{14}C-aliskiren 500, 100, and 3 mg/kg to male mice, male rats, and male marmosets, respectively, the fecal excretion of radioactivity up to 72, 96, and 168 hours post-dose was 88%, 94%, and 98% of the dose, respectively and the urinary excretion of radioactivity was 2%, 1%, and 5% of the dose, respectively.

3.(ii).A.(4).2) Biliary excretion (Attached document 4.2.2.2-3 and 4.2.2.4-1)

After oral administration of 100 mg/kg of ^{3}H-aliskiren to bile duct-cannulated male rats, 79% of the administered radioactivity was recovered within 72 hours. Thirteen percent, 64%, and 1.6% of the administered radioactivity were excreted in the bile, feces, and urine, respectively, showing that the primary route of excretion is in the bile and in the feces. After intravenous administration of 10 mg/kg of ^{14}C-aliskiren to male rats, 83% of the administered radioactivity was recovered within 24 hours and 70%, 5%, and 6% of the administered radioactivity were excreted in the bile, feces, and urine, respectively. When the collected bile was infused into the duodenum of other rats, 2.2% and 0.6% of the administered radioactivity were excreted in the bile and in the urine, respectively, within 48 hours, indicating that the enterohepatic circulation is negligible.

3.(ii).A.(4).3) Excretion in milk (Attached document 4.2.2.3-7)

After oral administration of 100 mg/kg of ^{14}C-aliskiren to lactating rats, radioactivity excreted in milk up to 72 hours after dosing accounted for about 0.08% of the administered dose.

3.(ii).A.(5) Pharmacokinetic drug interactions (Attached document 4.2.2.6-4, 4.2.2.5-1)

When 15 mg/kg of aliskiren was co-administered with 3, 15, and 30 mg/kg of ketoconazole to male rats, the C_{max} of unchanged aliskiren increased 7.6-, 2.7-, and 4.6-fold, respectively, compared to that in the control group (aliskiren plus vehicle group) and the $AUC_{0\text{-}t}$ per dose increased 3.8-, 2.5-, and 2.1-fold, respectively, compared to that in the control group.

When 15 mg/kg of aliskiren was co-administered with 6, 12.5, and 50 mg/kg of PSC833 (a P-glycoprotein inhibitor) to rats, the C_{max} and $AUC_{0\text{-}t}$ increased in a dose-dependent manner. The time to reach the maximum plasma drug concentration (t_{max}) was also delayed and the t_{max} was 8, 4, and 4 hours (median), respectively, as compared to 0.25 hours in the control group. Biliary excretion of aliskiren was inhibited.

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

PMDA asked the applicant to discuss the reason for a trend towards more than dose-proportional increases of AUC in a rat 2-week repeat-dose toxicity study, marmoset 13- and 39-week repeat-dose toxicity studies, etc. and the potential for this pharmacokinetic property to affect the toxicity in animals and the safety of an

increased dose in humans.

The applicant responded as follows:
More than dose-proportional increases in the AUC may be attributable to the saturation of P-glycoprotein due to extremely high doses used in these toxicity studies, which affected the excretion of aliskiren. In marmosets, as changes associated with the pharmacological effects of aliskiren including antihypertensive effects, increases in blood urea nitrogen (BUN) and serum creatinine were noted at ≥ 5 mg/kg/day, suggesting the effects on the renal function. Even when the exposure increased more than dose-proportionally in the high dose groups, the observed changes associated with the pharmacological effects of aliskiren were similar and increases in BUN and serum creatinine and hyperplasia of the juxtaglomerular apparatus of the kidneys were observed also at 20 mg/kg/day. In rats, although toxicities considered associated with the pharmacological effects as seen in marmosets were not noted, histological changes indicative of local gastrointestinal tract irritation (mucosal hyperplasia) were observed at ≥ 276 mg/kg/day of aliskiren. On the other hand, regarding the safety of an increased dose in humans, the nature and incidence of adverse events reported with 75 to 300 mg of aliskiren were similar to those with placebo, which probably indicates that the safety of a dose increase from 150 mg (the usual clinical dose) to 300 mg (the maximum clinical dose) has adequately been confirmed. Based on this finding, although the intra- and inter-individual variability of plasma aliskiren concentration is large, such variability within the clinical dose range is unlikely to affect the safety of aliskiren.

PMDA considers as follows:
Although the above-mentioned rat and marmoset repeat-dose toxicity studies were conducted at doses higher than the clinical dose on the basis of body weight, given that more than dose-proportional increases of AUC in the non-clinical studies are attributable to the saturation of P-glycoprotein, it cannot be excluded that the exposure of aliskiren may increase more than dose-proportionally also in humans via multiple mechanisms, e.g., reduced biliary excretion and increased gastrointestinal absorption. Whether the safety of aliskiren in humans within the clinical dose range has been adequately ensured will be further reviewed based on clinical study data.

3.(iii) Summary of toxicology studies

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

Single-dose toxicity, repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, local tolerance, and other toxicity studies were conducted.

3.(iii).A.(1) Single-dose toxicity (Attached document 4.2.3.1-1)

A single oral dose toxicity study in rats was a non-Good Laboratory Practice (GLP) study. Aliskiren hemifumarate was administered by oral gavage at a dose of 1000 or 2000 mg/kg to female rats. There were no abnormal clinical observations, nor were any changes observed in body weight. No abnormal necropsy findings were noted at 14 days after dosing. The approximate lethal dose was determined to be > 2000 mg/kg. The approximate lethal dose in this study was considered appropriate because no death occurred in

a comet assay (GLP study, Attached document 4.2.3.3.2-2) in which male rats were dosed twice by gavage with 1105 or 2210 mg/kg of aliskiren hemifumarate, with an interval of 21 hours between administrations.

Acute toxicity in non-rodents was discussed based on a rising dose toxicity study in marmosets (Attached document 4.2.3.2-16). Rising doses of 20 mg/kg/day for 4 days, 50 mg/kg/day for 4 days, and 100 mg/kg/day for 7 days were administered by oral gavage to males and females. No animals died and the approximate lethal dose was determined to be > 100 mg/kg.

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

3.(iii).A.(2).1) Repeat-dose toxicity studies in mice

(a) Two-week repeat-dose toxicity studies in mice (Attached document 4.2.3.2-1, -2, -3)

These studies were conducted in order to select the doses for long-term repeat-dose toxicity studies. Aliskiren hemifumarate (1000, 2000, 3000 mg/kg/day) was administered by oral gavage for 2 weeks to male and female mice. In the 2000 mg/kg/day group (9 males and 9 females) and the 3000 mg/kg/day group (18 males and 18 females), all mice died or were sacrificed moribund after the first dose. In the 1000 mg/kg/day group, 1 of 9 males and 1 of 9 females were sacrificed due to poor clinical condition, but a causal relationship to aliskiren was reported as unknown. Based on the above, the recommended maximum dose for long-term repeated oral dose toxicity studies in mice was determined to be 1000 mg/kg/day.

Aliskiren hemifumarate (150, 350, 800 mg/kg/day) was administered by oral gavage for 2 weeks to male and female mice and in the 150 mg/kg/day group, the dose was increased to 1200 mg/kg/day on Day 9. One of 6 males in the 350 mg/kg/day group and 1 of 6 females in the 800 mg/kg/day died. In the surviving animals receiving up to 800 mg/kg/day, there were no abnormalities in clinical signs, body weight, or food consumption. In the group where the dose was increased from 150 to 1200 mg/kg/day, 1 of 6 males was sacrificed due to poor clinical condition on the first day of dosing with 1200 mg/kg/day and the surviving animals showed decreased body weight. Histopathological examination revealed minimal to severe inflammatory changes in the nasal cavity at all dose levels of aliskiren. Based on the above, the no observed adverse effect level (NOAEL) was determined to be < 350 mg/kg/day.

Male and female mice were given aliskiren hemifumarate at doses of 150, 600, and 1000 mg/kg/day (by diet) or at a dose of 1000 mg/kg/day (by gavage) for 2 weeks. Because dietary administration of aliskiren hemifumarate resulted in very slight decreases in food consumption in males and females at 1000 mg/kg/day, the NOAEL was determined to be 600 mg/kg/day. After gavage administration of 1000 mg/kg/day, 1 of 6 males and 1 of 6 females died and histopathological examination revealed inflammation, necrosis, and ulceration of the respiratory epithelium of the nasal cavity. Since inflammatory changes in the respiratory system were noted, 1000 mg/kg/day of aliskiren was considered too high for a > 2-week oral gavage repeat-dose toxicity study.

(b) Four-week repeat-dose toxicity study in mice (Attached document 4.2.3.2-4)

Male and female mice were given aliskiren hemifumarate admixed with the diet at doses of 553, 1105, 1658, and 2210 mg/kg/day for 4 weeks. As changes in clinical observations, body weight gain was reduced in males at ≥ 1105 mg/kg/day and females at ≥ 1658 mg/kg/day. As changes in organ weights, decreases in uterine weights in females at ≥ 1658 mg/kg/day, decreases in ovarian weights in females at 2210 mg/kg/day, and decreases in weights of kidneys, spleens, and thymuses in males and females at 2210 mg/kg/day were observed. Histopathological examination revealed hypertrophy or hyperplasia of the duodenum, cecum, or jejunum mucosa in males and females at ≥ 1105 mg/kg/day, decreased density of uterine glands in females at ≥ 1658 mg/kg/day, and increased ovarian follicular atresia and absence of corpora lutea in females at 2210 mg/kg/day. Based on the above, the NOAEL was determined to be 553 mg/kg/day.

(c) Thirteen-week repeat-dose toxicity study in mice (Attached document 4.2.3.2-5)

This study was conducted in order to select the doses for carcinogenicity studies. Dietary administration of 1000, 2500, and 5000 mg/kg/day of aliskiren hemifumarate to male and female mice was initiated, but the dosing of the 2500 and 5000 mg/kg/day groups was stopped after a week of dosing due to decreases in body weight and food consumption. Dosing was resumed 2 weeks later at reduced levels of 1500 and 2000 mg/kg/day, respectively, from Day 22 onwards. In all groups, the duration of treatment (excluding the period during which dosing was suspended) was 13 weeks. Although 1 of 12 males in the 1000 mg/kg/day group died, as no similar changes were observed in other animals in the same dose group or in the higher dose groups, this death was considered unrelated to aliskiren. Slight increases in food consumption were noted in females at ≥ 1000 mg/kg/day, which was inferred to be attributable to feed spillage due to decreased palatability for feed admixture. Hematology findings included reductions in white blood cell count, lymphocyte count, plateletcrit, platelet volume, and platelet distribution width in males and females at ≥ 1500 mg/kg/day and decreases in platelet count in females at ≥ 1500 mg/kg/day. Clinical chemistry findings included decreases in glucose levels in females at ≥ 1000 mg/kg/day, decreases in total bilirubin levels and glucose levels in males at ≥ 1500 mg/kg/day, elevations of aspartate aminotransferase values in females at ≥ 1500 mg/kg/day, increases in BUN in males at 2000 mg/kg/day, and decreases in total bilirubin levels in females at 2000 mg/kg/day.

Based on the above, the NOAEL was determined to be < 1000 mg/kg/day and it was concluded that doses exceeding 2000 mg/kg/day are inappropriate for mouse carcinogenicity studies.

3.(iii).A.(2).2) Repeat-dose toxicity studies in rats

(a) Rising dose toxicity study in rats (Attached document 4.2.3.2-7)

Male and female rats were given aliskiren hemifumarate admixed with the diet at increasing doses of 1105, 1658, 2210, and 2763 mg/kg/day for 2 weeks/dose level. Soft feces at ≥ 2210 mg/kg/day and reduced food consumption at all dose levels were observed. Dose-dependent reductions in body weight gain were noted at all dose levels. There were no aliskiren-related findings observed at necropsy or histopathological

examination and the maximum tolerated dose of aliskiren hemifumarate was determined to be 2763 mg/kg/day.

(b) Two-week repeat-dose toxicity study in rats (Attached document 4.2.3.2-8)

Male and female rats were given aliskiren hemifumarate by oral gavage at doses of 100, 300, and 1000 mg/kg/day for 2 weeks. At 1000 mg/kg/day, 2 of 5 males and 2 of 5 females died or were sacrificed due to poor clinical condition. As changes in clinical observations, body weight loss in females and decreased food consumption in males at 1000 mg/kg/day were observed. As changes in organ weights, slight decreases in liver weights in males at ≥ 300 mg/kg/day and slight decreases in heart weights in females at 1000 mg/kg/day were noted. Necropsy of the animals that died or were sacrificed revealed gaseous distension of the stomach, small intestine, and large intestine and smaller thymus, spleen, axillary lymph nodes, and mesenteric lymph nodes and histopathological examination showed minimal to mild inflammation in the small and large intestines, lymphangiectasia, lymph fluid congestion and mucosal atrophy, thymus and spleen atrophy, and lymphopenia in the axillary and mesenteric lymph nodes. Based on the above, the NOAEL was determined to be 100 mg/kg/day.

(c) Two-week repeat-dose toxicity studies in rats (Attached document 4.2.3.2-9, -10)

Male and female SD and Wistar rats were given aliskiren hemifumarate by oral gavage at doses of 66, 221, and 663 mg/kg/day for 2 weeks.

In SD rats, 1 of 10 males and 1 of 10 females in the 663 mg/kg/day group died, but the cause of death could not be identified. As changes in clinical observations, soft feces were observed in males and females at 663 mg/kg/day. Clinical chemistry findings included increases in total cholesterol and phospholipids in males and increases in β-globulin and decreases in albumin, α2-globulin, and albumin/globulin (A/G) ratio in females at ≥ 221 mg/kg/day. Based on the above, the NOAEL was determined to be 66 mg/kg/day.

In Wistar rats, 3 of 10 males and 1 of 10 females in the 663 mg/kg/day group died and based on the results of histopathological examination, it was inferred that the deaths were attributed to aspiration of the dosing solution into the respiratory tract and its associated secondary changes. As changes in clinical observations, soft feces in males, reductions in body weight gain in females, and decreases in food consumption in males and females at 663 mg/kg/day were observed. Clinical chemistry findings included increases in β-globulin in males and females, elevations of γ-glutamyl transferase (γ-GTP) in males, and increases in phosphorus and decreases in total protein, albumin, and A/G ratio in females at 663 mg/kg/day. As changes in organ weights, decreases in liver and kidney weights were noted in males at 663 mg/kg/day. At histopathological examination, inflammatory changes in the nasopharynx, nasal cavity, larynx, trachea, and lung were seen in the dead animals in the 663 mg/kg/day group. Furthermore, inflammatory changes in the gastrointestinal tract, hypertrophy of the adrenal cortex, lymphopenia in mesenteric lymph nodes and spleen, atrophy of hepatocytes, and myocardial necrosis, indicative of deterioration of the clinical condition, were also noted. As histological changes in the surviving animals, minimal tubular cast formation in the kidney, slight vacuolation and minimal dilatation of the renal tubule, moderate vasodilation in the corticomedullary

junction, and increases in protein-like material in the Bowman's capsule were found sporadically, but their relationship to aliskiren was unclear. Based on the above, the NOAEL was determined to be 221 mg/kg/day.

(d) Two-week repeat-dose (dietary/gavage) toxicity study in rats (Attached document 4.2.3.2-11)

Male and female rats were given aliskiren hemifumarate at doses of 1000, 1750, or 2500 mg/kg/day (in the diet) or at doses of 1000, 2000, or 4000 mg/kg/day (by gavage) for 2 weeks. Following dietary administration, 1 of 5 males died at 2500 mg/kg/day. As changes in clinical observations, emaciation, stained fur, and hunched position in males and females at 2500 mg/kg/day, reductions in body weight gain in males at ≥ 1750 mg/kg/day and in females at 2500 mg/kg/day, and marked decreases in food consumption in males and females at ≥ 1750 mg/kg/day were observed. Hematology findings included increases in hemoglobin in males at ≥ 1750 mg/kg/day and decreases in reticulocyte count in males at 1000 mg/kg/day and in males and females at ≥ 1750 mg/kg/day and clinical chemistry findings included decreases in alkaline phosphatase (ALP) in males at ≥ 1750 mg/kg/day. As changes in organ weights, decreases in spleen, liver, thymus, epididymis, and prostate gland weights in males and decreases in uterine weights in females at ≥ 1750 mg/kg/day were observed. Necropsy revealed emaciation and smaller thymus in males and females and smaller testis, epididymis, seminal vesicle, and prostate gland in males at 2500 mg/kg/day. Histopathological examination revealed fat atrophy, hypertrophy of the peri-insular acini of the pancrea, bone marrow hypocellularity, congestion, and thymic cortical atrophy in males and females, atrophy of or decreased secretion from the testis, epididymis, prostate gland, and seminal vesicle in males, and splenic lymphatic atrophy in females at 2500 mg/kg/day. Following gavage administration, all animals in the 4000 mg/kg/day group were sacrificed due to poor clinical condition on Day 2 and histopathological examination revealed acute inflammation and ulceration of the glandular stomach. At 2000 mg/kg/day, 3 of 5 males and 1 of 5 females were sacrificed due to poor clinical condition and histopathological examination showed changes in the renal tubule in 2 males and acute inflammation and ulceration of the glandular stomach in 1 female, whereas the cause of poor clinical condition in the 1 male was unknown. At 1000 mg/kg/day, 1 of 5 females was sacrificed due to poor clinical condition and as histological changes, necrosis and ulceration of the respiratory epithelium of the nasal cavity were noted. As changes in clinical observations, salivation at all dose levels, paddling, stained fur, soft feces, watery diarrhea, ptosis, and hunched position in males and females at ≥ 2000 mg/kg/day, and marked decreases in food consumption in males and females at 2000 mg/kg/day were observed. Hematology findings included decreases in red blood cell parameters in females at 2000 mg/kg/day and clinical chemistry findings included increases in total cholesterol and glucose levels and decreases in BUN in males and decreases in total bilirubin and increases in total protein and globulin in females at ≥ 1000 mg/kg/day. As changes in organ weights, increases in ovarian weights in females at ≥ 1000 mg/kg/day and decreases in thymic weights in males and decreases in uterine weights in females at 2000 mg/kg/day were observed. Necropsy of the surviving animals revealed emaciation in males and females at 2000 mg/kg/day and morphological changes and discoloration of the gastrointestinal tract in males and females at ≥ 2000 mg/kg/day. Histopathological examination of the surviving animals showed no aliskiren-related changes. Based on the above, the NOAEL was determined to be < 1000 mg/kg/day for both dietary and gavage administration.

(e) Thirteen-week repeat-dose (dietary/gavage) toxicity study in rats (Attached document 4.2.3.2-12)

This study was conducted in order to determine the mode of administration for carcinogenicity studies. Male and female rats were given aliskiren hemifumarate at doses of 829 and 1105 mg/kg/day (by diet) or at doses of 553 and 829 mg/kg/day (by gavage) for 13 weeks.

Following gavage administration, 3 of 10 males and 2 of 10 females in the 553 mg/kg/day group and 4 of 10 males and 6 of 10 females in the 829 mg/kg/day group died. Because histopathological examination revealed inflammatory changes in the nasal cavities and larynx, these deaths were inferred to be related to aspiration of the dosing solution into the respiratory tract. As changes in clinical observations, prone position in males and females at 553 mg/kg/day, labored respiration, rales, and poor clinical condition in males and females at ≥ 553 mg/kg/day, and emaciation in males and females and tachypnea in males at 829 mg/kg/day were observed. Necropsy showed no aliskiren-related changes. Histopathological examination revealed inflammatory exudates and ulceration in the nasal cavities and nasopharynx in males and females in all groups, inflammatory exudates and ulceration in the larynx in all groups excluding females in the 553 mg/kg/day group, and erosion in the cecum and ulceration in the colon in females at 829 mg/kg/day. As changes in organ weights, decreases in liver weights were observed in males in all groups, but necropsy revealed no aliskiren-related changes.

Following dietary administration, decreases in liver weights were observed in males in all groups, but necropsy revealed no aliskiren-related changes.

In a toxicokinetic study, after 13 weeks of dietary administration, systemic exposure to aliskiren increased with the dose in males, but not in females, suggesting saturation of absorption. After single or 13-week repeated gavage administration, systemic exposure to aliskiren in both males and females increased with the dose. Exposures attained by gavage were higher than those attained by feeding and after 13 weeks of dosing, the $AUC_{0\text{-}24h}$ was 8106 ng·h/mL in the 829 mg/kg/day gavage group, which was about 2-fold higher than 4171 ng·h/mL in the 1105 mg/kg/day feeding group.

Based on the above, the NOAEL was determined to be 1105 mg/kg/day for dietary administration and < 553 mg/kg/day for gavage administration and it was concluded that oral gavage is not appropriate as the mode of administration for carcinogenicity studies.

(f) Thirteen-week repeat-dose toxicity study in rats (Attached document 4.2.3.2-13)

Male and female rats were given aliskiren hemifumarate by oral gavage at doses of 60, 200, or 600 mg/kg/day for 13 weeks. Three of 15 males and 4 of 15 females in the 200 mg/kg/day group and 2 of 15 males and 8 of 15 females in the 600 mg/kg/day group died or were sacrificed due to poor clinical condition. As changes in clinical observations in the animals that died or were sacrificed, rales and salivation were noted in males and females at ≥ 200 mg/kg/day. Histopathological examination revealed

minimal to mild hypertrophy or hyperplasia of the cecum mucosa in males at 200 mg/kg/day and in males and females at 600 mg/kg/day. Even after a 4-week recovery period, minimal hypertrophy or hyperplasia of the cecum mucosa was observed in males at 600 mg/kg/day. Necropsy and histopathological examination of the animals that died or were sacrificed showed inflammatory changes in the trachea and lungs, indicative of aspiration of the dosing solution, and congestion in the heart, liver, and kidney. Based on the above, the NOAEL was determined to be 60 mg/kg/day.

(g) Twenty-six week repeat-dose toxicity study in rats (Attached document 4.2.3.2-14)

Male and female rats were given aliskiren hemifumarate by oral gavage at doses of 50, 150, or 250 mg/kg/day for 26 weeks. As changes in clinical observations, hunched posture and noisy breathing were observed in males and females at 250 mg/kg/day, which were both as anticipated from the irritant properties of aliskiren, and dosing of these animals with symptoms was suspended until recovery. Paddling and straub tail were noted in males and females at ≥ 150 mg/kg/day. Histopathological examination revealed bronchoalveolar epithelial hyperplasia in the lungs in males and females at 150 mg/kg/day and in males at 250 mg/kg/day and epithelial hyperplasia and granulation etc. at the tracheal bifurcation in males and females at 250 mg/kg/day. Based on the above, the NOAEL was determined to be 50 mg/kg/day.

(h) One-week repeated intravenous dose toxicity study in rats (Attached document 4.2.3.2-15)

Male and female rats were given aliskiren hemifumarate at doses of 1, 3, or 10 mg/kg/day intravenously for 9 to 12 days. Because 1 of 5 males in the 10 mg/kg/day group died on Day 1, the dose was reduced to 7.5 mg/kg/day from Day 2 onwards. As changes in clinical observations, body weight was decreased in males and females at 7.5 mg/kg/day. Based on the above, the NOAEL was determined to be 3 mg/kg/day.

3.(iii).A.(2).3) Repeat-dose toxicity studies in marmosets

(a) Two-week repeat-dose toxicity study in marmosets (Attached document 4.2.3.2-17)

Male and female marmosets were given aliskiren hemifumarate by oral gavage at doses of 10, 50, or 100 mg/kg/day for 2 weeks. As changes in clinical observations, vomiting and diarrhoea in males and females and salivation in males at 100 mg/kg/day were noted. Reduced food consumption was observed at all dose levels of aliskiren and 1 of 2 females in the 100 mg/kg/day group exhibited body weight loss. Clinical chemistry findings included increased levels of BUN, creatinine, and magnesium in males and females at ≥ 50 mg/kg/day and increased ALP in 1 of 2 females at 100 mg/kg/day. Histopathological examination revealed arteriolar hypertrophy in the kidneys in 1 of 2 females and single cell necrosis of the liver in the other female at 100 mg/kg/day. Based on the above, the NOAEL was determined to be 10 mg/kg/day.

(b) Thirteen-week repeat-dose toxicity study in marmosets (Attached document 4.2.3.2-18)

Male and female marmosets were given aliskiren hemifumarate by oral gavage at doses of 5, 20, or 50 mg/kg/day for 13 weeks. One of 3 females receiving 20 mg/kg/day and 1 of 5 females receiving 50 mg/kg/day were sacrificed due to poor clinical condition. As changes in clinical observations, an increased incidence of salivation, vomiting, and diarrhoea in males and females at 50 mg/kg/day and slight body weight loss in females at ≥ 20 mg/kg/day were observed, which were all reversible after a 4-week recovery

period. Histopathological examination revealed arteriolar hypertrophy in the kidney cortices in females at 5 mg/kg/day and in males and females at ≥ 20 mg/kg/day, which was still evident following the recovery period. The sacrificed animals showed dilatation and degeneration or regeneration of cortical tubules of the kidney. Based on the above, the NOAEL was determined to be 5 mg/kg/day for males and < 5 mg/kg/day for females.

(c) Thirty-nine week repeat-dose toxicity study in marmosets (Attached document 4.2.3.2-19)

Male and female marmosets were given aliskiren hemifumarate by oral gavage at doses of 2, 5, or 20 mg/kg/day for 39 weeks. One of 5 males and 1 of 5 females in the 5 mg/kg/day group and 1 of 5 males in the 20 mg/kg/day group died or were sacrificed due to poor clinical condition. The cause of death for these animals included acute pneumonia, peritonitis, pleuritis, and ulceration of the cecum or rectum and none of these deaths was attributable to an effect of aliskiren. As changes in organ weights, increases in liver and kidney weights were noted in males at 20 mg/kg/day. Histopathological examination of the surviving animals revealed minimal to slight hyperplasia of the juxtaglomerular apparatus of the kidneys in 2 of 5 males and 1 of 5 females and slight to moderate interstitial inflammation of the kidneys in 1 of 5 males and 1 of 5 females at 20 mg/kg/day. All changes were reversible after a recovery period. Based on the above, the NOAEL was determined to be 2 mg/kg/day.

3.(iii).A.(3) Genotoxicity

As genotoxicity studies, bacterial reverse mutation assay (Attached document 4.2.3.3.1-2, -3), gene mutation test with V79 cells (Attached document 4.2.3.3.1-4), chromosomal aberration assay in CHO cells (Attached document 4.2.3.3.1-5, -6), oral micronucleus assay in rats (Attached document 4.2.3.3.2-1), and comet assay in rats (Attached document 4.2.3.3.2-2) were performed. The results of these tests indicated no genotoxic potential of aliskiren.

3.(iii).A.(4) Carcinogenicity

3.(iii).A.(4).1) Twenty-six week carcinogenicity study in transgenic mice for short-term carcinogenicity testing (Attached document 4.2.3.4.2-1)

Male and female mice for short-term carcinogenicity testing (CB6F1/Jic-TgrasH2@Tac hemizygous) were given aliskiren hemifumarate admixed with the diet at doses of 276, 829, and 1658 mg/kg/day for 26 weeks. Males and females in the 1658 mg/kg/day group exhibited a transient decrease in food consumption and body weight loss during the early phase of dosing. The overall food intake was slightly reduced in males and females at ≥ 829 mg/kg/day. The nonneoplastic lesions observed were diffuse mucosal hypertrophy in the cecum in males and females at ≥ 829 mg/kg/day and cytoplasmic inclusions in the respiratory epithelia of the nasal cavity, macrophage accumulation and inflammation in the lung, diffuse mucosal hypertrophy in the duodenum, focal atypical hyperplasia of the colon, and gallbladder dilatation in males and females and bone marrow hypocellularity, endometrial atrophy, and an absence and decrease of corpora lutea in females at 1658 mg/kg/day. On the other hand, the study results indicated no carcinogenic potential of aliskiren and the NOAEL was determined to be 276 mg/kg/day.

3.(iii).A.(4).2) 104-week carcinogenicity study in rats (Attached document 4.2.3.4.1-1)

Male and female rats were given aliskiren hemifumarate admixed with the diet at doses of 276, 829, or 1658 mg/kg/day for 104 weeks. No increases in the incidence of palpable masses were noted in the aliskiren groups compared to the control group. As changes in clinical observations, perineal staining in males and females at 276 and ≥ 829 mg/kg/day, fecal abnormalities and an increased incidence of feed spillage in males and females at ≥ 829 mg/kg/day, emaciation in males at 829 mg/kg/day and in males and females at 1658 mg/kg/day, hunched posture in males at ≥ 829 mg/kg/day, and unkept coat in males and females at 1658 mg/kg/day were observed. Dose-dependent reductions in body weight gain were observed at all dose levels of aliskiren and food consumption was decreased in females at 276 mg/kg/day and in males and females at 829 mg/kg/day. Accurate evaluation of food consumption at 1658 mg/kg/day was not possible due to a high incidence of feed spillage. The reductions in body weight gain were considered related to decreased food consumption. Necropsy revealed cystic mesenteric lymph nodes in males at ≥ 829 mg/kg/day. Although there were no significant differences in the incidence of tumor lesions between the aliskiren and control groups, a colonic adenoma was found in one male and a cecal adenocarcinoma in another male among the 60 rats receiving 1658 mg/kg/day. A relationship of these tumors to aliskiren could not be ruled out, since the incidence of large intestinal adenoma/adenocarcinoma in historical controls (rodents) is low. Inflammatory and proliferative changes in the intestines were noted at both the 52-week and 104-week sacrifices. At the 52 weeks sacrifice, an increased incidence of mucosal epithelial hyperplasia of the cecum and colon at ≥ 829 mg/kg/day and an increased incidence of dilation of sinusoids in mesenteric lymph nodes and an increased severity of aggregates of macrophages in males at 829 mg/kg/day and in males and females at 1658 mg/kg/day were observed. Since inflammatory changes in the intestines and sinusoidal dilatation and macrophage aggregates in mesenteric lymph nodes increased in a dose-dependent manner, the inflammatory and proliferative changes in the intestines were considered secondary to the irritant properties of aliskiren. Based on the above, the NOAEL for gastrointestinal effects was determined to be 276 mg/kg/day.

3.(iii).A.(5) Reproductive and developmental toxicity

3.(iii).A.(5).1) Rat study of fertility and early embryonic development to implantation (Attached document 4.2.3.5.1-1)

Aliskiren hemifumarate was administered orally by gavage to male and female rats at doses of 50, 150, or 250 mg/kg/day for 2 weeks prior to mating and throughout the mating period until the day before necropsy for males and until day 6 of gestation for females. As changes in clinical observations, females in the 150 mg/kg/day group and males and females in the 250 mg/kg/day group showed salivation immediately after dosing and males and females at ≥ 150 mg/kg/day exhibited paddling and rubbing of the mouth/face against the cage immediately after dosing. Aliskiren hemifumarate did not affect fertility or early embryonic development. Based on the above, the NOAELs were determined to be 50 mg/kg/day for general toxicity of parent animals and 250 mg/kg/day for reproductive and developmental toxicity of parent animals and for early embryonic development.

3.(iii).A.(5).2) Rat embryo-fetal development study (Attached document 4.2.3.5.2-1)

Aliskiren hemifumarate was administered orally by gavage to pregnant rats at doses of 60, 300, or 600 mg/kg/day on gestational days 6 through 17. As changes in clinical observations in maternal animals during the dosing period, decreased and soft stool at doses ≥ 60 mg/kg/day, salivation and decreased food consumption at doses ≥ 300 mg/kg/day, and diarrhoea and reduced body weight gain at 600 mg/kg/day were observed. Effects on embryo-fetal development or teratogenic effects were not observed. Based on the above, the NOAEL for maternal general toxicity was determined to be < 60 mg/kg/day and the NOAEL for maternal reproductive and developmental toxicity or fetal toxicity was determined to be 600 mg/kg/day.

3.(iii).A.(5).3) Rabbit embryo-fetal development study (Attached document 4.2.3.5.2-4)

Aliskiren hemifumarate was administered orally by gavage to pregnant rabbits at doses of 50, 100, or 200 mg/kg/day on gestational days 7 through 28. Because 7 of 24 maternal animals in the 200 mg/kg/day group died or were sacrificed due to poor clinical condition between gestation days 13 and 18, the surviving animals were sacrificed between gestation days 11 and 21. One of 22 animals in the 50 mg/kg/day group and 3 of 22 animals in the 100 mg/kg/day group died. As changes in clinical observations, emaciation at 100 mg/kg/day and reductions in body weight gain, food consumption, and water consumption at ≥ 50 mg/kg/day were observed. Effects on embryo-fetal development or teratogenic effects were not observed. Based on the above, the NOAEL for maternal general toxicity was determined to be < 50 mg/kg/day and the NOAEL for maternal reproductive and developmental toxicity or fetal toxicity was determined to be 100 mg/kg/day.

3.(iii).A.(5).4) Rat study for effects on pre- and postnatal development, including maternal function (Attached document 4.2.3.5.3-1)

Aliskiren hemifumarate was administered orally by gavage to pregnant rats at doses of 50, 150, or 250 mg/kg/day on gestation day 6 through lactation day 21. As changes in clinical observations, animals at ≥ 150 mg/kg/day exhibited paddling and rubbing of the mouth/face against the cage immediately after dosing on gestation day 21 through lactation day 21. There were no effects on the development or reproductive performance of the F1 generation. Based on the above, the NOAEL for maternal general toxicity was determined to be 50 mg/kg/day and the NOAEL for maternal reproductive and developmental toxicity or pups was determined to be 250 mg/kg/day.

3.(iii).A.(6) Local tolerance (Attached document 4.2.3.6-1, -5)

The local tolerance of aliskiren was evaluated in an *in vitro* hemolysis test with human blood and a vascular irritation study in rabbits. Aliskiren caused no hemolysis or vascular irritation.

3.(iii).A.(7) Other toxicity studies

3.(iii).A.(7).1) Immunotoxicity (Attached document 4.2.3.2-14, 4.2.3.7.2-1, -2)

The immunotoxicity of aliskiren was evaluated in a 26-week repeat-dose toxicity study in rats. Fluorescein activated cell sorter (FACS) analysis of T-cells, B-cells, and NK cell markers showed no changes in

lymphocyte phenotype, nor there were any histological changes in the immune system organs, indicative of the immunotoxicity of aliskiren.

A murine local lymph node assay (LLNA) was performed to evaluate the contact allergenic potential of aliskiren. In LLNA (Tier I), aliskiren was classified as a chemical with a weak lymph node activation and skin irritation potential. In LLNA (Tier II), aliskiren-induced contact allergy-like skin reactions were observed, but changes in lymphocytes characteristic of a contact allergic reaction were not detected in the draining lymph nodes and it was concluded that aliskiren is not a skin sensitizer.

3.(iii).A.(7).2) Studies on impurities (Attached document 4.2.3.7.6-1 - 9)

The safety of impurities were evaluated in repeat-dose toxicity and genotoxicity studies, which qualified the acceptance criteria of all impurities.

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

Taking into account that the relationship of the tumor lesions observed in a 104-week carcinogenicity study in rats (Attached document 4.2.3.4.1-1) to aliskiren could not be ruled out, the applicant explained about the carcinogenic risk of aliskiren as follows:

In 4-week and 13-week repeat-dose mechanistic studies in rats (Attached document 4.2.3.7.3-5, -8), the fecal aliskiren concentrations at 276 mg/kg/day (the NOAEL dose in the carcinogenicity study) were 16940 and 10958 μg/g, respectively, which were approximately 7- to 11-fold higher than the human fecal aliskiren concentration at the maximum recommended human dose of 300 mg (1527 μg/g [Study 2105]). In a 1-week repeat-dose mechanistic study in rats (Attached document 4.2.3.7.3-3), the tissue concentrations of aliskiren in the jejunum, ileum, cecum, and colon were 70.5, 99.3, 135, and 132 μg/g, respectively, which were approximately 3- to 6-fold higher than the human rectal tissue concentration of aliskiren at the maximum recommended human dose of 300 mg (22.2 μg/g [Study 2105]). Furthermore, in an *in vitro* study using isolated colon preparations (Attached document 4.2.3.7.3-2), tissue conductance was determined in isolated rat and human colon preparations. As a result, although aliskiren (mucosal side, 10 mM; serosal side, 1 mM) increased tissue conductance in rat colon preparations, a similar effect was not noted in human colon preparations, suggesting that rat colon tissue is more sensitive to the local irritant effects of aliskiren than human colon tissue. Based on the above results, it can be inferred that the true safety margin of aliskiren in humans is even wider than that in rats. In addition, since a standard battery for genotoxicity testing in accordance with the Attachment to “Guideline for Genotoxicity Testing of Pharmaceuticals” (PMSB/ELD Notification No. 1604 dated November 1, 1999) and a comet assay in rats indicated no genotoxic potential of aliskiren, it has been discussed that the human carcinogenic risk of aliskiren in clinical use is low.

PMDA considered as follows:

Although the above explanation is understandable in some aspects, taking also into account that a foreign clinical study to evaluate the risk of colorectal hyperplasia in humans is currently ongoing, the applicant should continue to pay attention to colorectal hyperplasia associated with aliskiren, including future

information [see “4.(iii).B.(3).3) Colorectal hyperplasia”].

Taking into account that on a body weight basis, the proposed clinical doses (75-300 mg/day) exceed the NOAEL dose (2 mg/kg/day) in a 39-week repeat-dose toxicity study in marmosets (Attached document 4.2.3.2-19), PMDA asked the applicant to discuss the clinical significance of the effects on the kidneys observed in repeat-dose toxicity studies in marmosets.

The applicant responded as follows:
The changes in the kidneys observed in marmosets were predominantly minimal to slight in severity and were reversible after a recovery period except for arteriolar hypertrophy. Dilatation and degeneration/regeneration of renal tubules and arteriolar hypertrophy are considered attributable to decreases in blood pressure and renal perfusion associated with the pharmacological effects of aliskiren and hyperplasia of the juxtaglomerular apparatus is inferred to be due to hypertrophy/proliferation of renin-secreting cells surrounding the arteriole in the juxtaglomerular apparatus, resulting from aliskiren-induced renin inhibition and its associated compensatory increase in renin production. All of these changes have been reported in non-clinical studies with ACE inhibitors or Ang II receptor antagonists (ARB) (Dominick MA et al. *Toxicologic Pathology.* 1990;18:396-406, Owen RA et al. *Laboratory investigation.* 1994;71:543-51) and are considered to be known effects with antihypertensive agents acting on the RAS. In a 39-week repeat-dose toxicity study in marmosets (at doses of 2, 5, and 20 mg/kg/day), the exposure at the NOAEL dose (2 mg/kg/day) (mean $AUC_{0\text{-}24h}$ in males and females, 376 ng·h/mL) was lower than the human exposure at the maximum recommended human dose of 300 mg (2135 ng·h/mL [Foreign Study 2202]) while the exposure at 20 mg/kg/day (mean $AUC_{0\text{-}24h}$ in males and females, 17 633 ng·h/mL) was about 8-fold higher than the human exposure at 300 mg. The change observed at 20 mg/kg/day was decreased renal function due to reduced blood pressure associated with the pharmacological effects of aliskiren and at 5 mg/kg/day, slight increases in BUN and creatinine were noted but there were no histological changes in the kidneys. Furthermore, because no serious adverse events of renal dysfunction have been reported following 8-week administration of 600 mg in Foreign Study 2308, the changes in the kidneys as observed in normal marmosets that develop hypotension following the administration of aliskiren are unlikely to occur in humans who receive aliskiren for the treatment of hypertension.

PMDA accepted the response and concluded that there are no particular problems with toxicity studies.

4. Clinical data

4.(i) Summary of biopharmaceutic studies

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

4.(i).A.(1) Bioequivalence (BE) between different formulations

As the market formulation (MF) of aliskiren, an uncoated tablet (MF uncoated tablet) and a film-coated tablet (MF tablet) were first developed. The MF tablet was used in Foreign Study 2202. The MF uncoated

tablet or MF tablet was enclosed in a hard gelatin capsule for blinding purposes, which was used in Japanese Study 1101 and Foreign Studies 2202, 2209, and 2343.

On the other hand, the final market image (FMI) tablet (the color of the film coating of MF tablet has been changed) was used in all Japanese clinical studies except for Japanese Study 1101 (Studies 1102, 1104, 1201, 1202, 1301, 1303, 1304, 2324) and foreign clinical studies including Foreign Study 2308. In view of the above, bioequivalence (BE) review focused on the BE between different strengths of FMI used in Japanese clinical studies and the BE between over-encapsulated MF and FMI tablets.

4.(i).A.(1).1) BE between 75-mg FMI tablet and 150-mg FMI tablet

While the content of [redacted] in the coating was different between the 75-mg FMI tablet and the 150-mg FMI tablet, [redacted] and [redacted] in the tablet core were the same. Hence, the applicant compared the results of dissolution test and explained that these two formulations are bioequivalent.

4.(i).A.(1).2) Foreign BE study of over-encapsulated MF (150-mg tablet) and FMI (150-mg tablet) (Attached document 5.3.1.2-1, Study 2343 [[redacted] to [redacted] 20[redacted]])

A two-treatment, four-period, crossover study was conducted in 58 foreign healthy adult volunteers (41 male subjects, 17 female subjects) (with a 5-day washout period). Following a single oral dose of 150 mg of aliskiren under fasting conditions, the geometric mean ratios (GMR) for the $AUC_{0\text{-}t}$ and C_{max} of aliskiren (over-encapsulated MF/FMI) were 0.87 (0.81-0.95, 90% confidence interval [CI]) and 0.79 (0.69-0.89), respectively. The GMR for $AUC_{0\text{-}t}$ met the BE criteria of the Japanese guideline (0.80-1.25), but the GMR for C_{max} did not meet the BE criteria.

4.(i).A.(2) Absolute BA study (Attached document 5.3.1.1-4, Study 0029 [[redacted] to [redacted] 20[redacted]], Reference data)

A three-treatment, three-period, crossover study was conducted in 9 foreign healthy adult male volunteers (with a 14-day washout period). Following a single intravenous dose (given over 20 minutes) of 20 mg of aliskiren or a single oral dose of 75 mg (Speedel capsule [37.5 mg × 2] or oral solution) under fasting conditions, the C_{max} of aliskiren was 2086.7 ± 715.4 (mean ± SD), 27.7 ± 12.7, and 15.1 ± 7.9 ng/mL, respectively, the $AUC_{0\text{-}inf}$ was 2318.8 ± 611.5, 225.3 ± 102.0, and 158.2 ± 53.7 ng·h/mL, respectively, and the $t_{1/2}$ was 23.7 ± 7.6, 24.7 ± 7.1, and 25.8 ± 12.6 hours, respectively. The absolute BA of Speedel capsule and of oral solution were calculated to be 2.6 ± 0.8% and 1.9 ± 0.7%, respectively. After intravenous administration, the plasma clearance was 2.1 ± 0.6 mL/min/kg, the hepatic clearance was 1.9 ± 0.5 mL/min/kg, and the renal clearance (CL_r) was 0.15 ± 0.04 mL/min/kg. The elimination phase distribution volume was 4.1 ± 1.4 L/kg.

4.(i).A.(3) Food effect studies

4.(i).A.(3).1) Japanese clinical study (Attached document 5.3.1.1-1, Study 1102 [[redacted] to [redacted] 20[redacted]])

A two-treatment, two-period, crossover study was conducted in 34 Japanese healthy adult male volunteers (with a 10-day washout period). A 150-mg FMI tablet was orally administered once daily for 7 days in the fasted state (30 minutes before a meal) or after a meal. The median t_{max} values on Day 1 and Day 7 were 0.4 and 0.4 hours, respectively, in the fasted state and 2.0 and 1.0 hours, respectively, in the fed state and there was a trend towards delayed t_{max} after fed administration compared to fasted administration. The AUC_{0-t} values of aliskiren were 218 ± 153 (mean ± SD) and 1100 ± 469 ng·h/mL, respectively, in the fasted state and 70.2 ± 59.7 and 509 ± 316 ng·h/mL, respectively, in the fed state, and the C_{max} values were 83.5 ± 51.2 and 122 ± 86.1 ng/mL, respectively, in the fasted state and 19.3 ± 34.9 and 37.0 ± 46.6 ng/mL, respectively, in the fed state, and the AUC_{0-t} and C_{max} on Day 1 decreased by 69% and 84%, respectively, in fed subjects compared to fasted subjects and the AUC_{0-t} and C_{max} following repeated administration decreased by 55% and 75%, respectively, in fed subjects compared to fasted subjects.

4.(i).A.(3).2) Foreign clinical study (Attached document 5.3.1.1-2, Study 2207 [to 20], Reference data)

A two-treatment, two-period, crossover study was conducted in 32 foreign healthy adult volunteers (16 male subjects, 16 female subjects) (with a 10-day washout period). Following a single oral dose of a 300-mg FMI tablet in the fasted state or after a high-fat meal, the median t_{max} was 2.0 hours in the fasted state and 3.0 hours in the fed state. The AUC_{0-t} values of aliskiren in the fasted and fed states were 2315 ± 1165 and 707 ± 434 ng·h/mL, respectively, and the C_{max} values were 453.2 ± 308.5 and 92.4 ± 95.2 ng/mL, respectively, and the AUC_{0-t} and C_{max} decreased by 72% and 85%, respectively, in the fed state compared to the fasted state.

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

4.(i).B.(1) BE between different formulations

In Foreign Study 2343, the 90% confidence interval of the GMR for C_{max} did not meet the BE criteria of the Japanese guideline. The applicant explained as follows:

Since the FMI tablet was used in Japanese clinical studies excluding a single-dose study in Japanese healthy subjects (Japanese Study 1101) (the over-encapsulated MF uncoated tablet of 75 mg strength was used), even though the GMR for C_{max} of the over-encapsulated MF tablet to the FMI tablet did not meet the BE criteria, safety evaluation in Japanese healthy subjects is not significantly affected.

PMDA considered as follows:

Because there is no dissolution study directly comparing the dissolution behaviour between the over-encapsulated MF uncoated tablet and FMI tablet of 75 mg strength, the BE between these two formulations cannot be demonstrated. However, the FMI tablet was used in all Japanese clinical studies excluding Japanese Study 1101 (a single-dose study). Even though the GMR for C_{max} of the formulation used in Japanese Study 1101 to the FMI tablet does not meet the BE criteria of the Japanese guideline, such results does not significantly affect the evaluation of clinical study data or approval decision for aliskiren.

It cannot be concluded that the BE between the 75-mg FMI tablet and the 150-mg FMI tablet has been

demonstrated based on the dissolution data submitted by the applicant. However, because the applicant has suggested the withdrawal of the application for aliskiren 75-mg tablets [see 4.(iii).B.(2).2).(b) "75 mg (dose reduction as appropriate)"] and the 150-mg FMI tablet only was used in the 150 and 300 mg groups in Japanese phase II (Study 1201) and phase III (Study 1301) studies, this may not pose a major problem affecting the approval decision for aliskiren and the final conclusion on the BE between these formulations will be reported in the Review Report (2).

4.(i).B.(2) Food effect

Regarding the BA of aliskiren, C_{max} increased ≥ 3-fold and AUC increased ≥ 2-fold in the fasted state compared to the fed state (after repeated administration) and clinical studies have suggested that high-dose aliskiren may increase the risk of diarrhoea etc., which are considered also by the applicant to deserve special attention. From a safety point of view, PMDA asked for the applicant's view on whether or not to recommend taking aliskiren after a meal in the Dosage and Administration section of the package insert.

The applicant responded as follows:

In Japanese Study 1301, 2 of 3 subjects with diarrhoea at 150 mg of aliskiren had trough plasma aliskiren concentrations that were lower than the mean trough plasma aliskiren concentration in the overall study population and diarrhoea did not occur in subjects with extremely high trough plasma concentrations, showing no trend towards an association between plasma aliskiren concentrations and the development of diarrhoea. In Japanese Study 1102 (150 mg administered once daily for 7 days), the incidence of adverse events was 60.6% (20 of 33 subjects) after fasted administration and 41.2% (14 of 34 subjects) after fed administration, but the incidence of each adverse event was comparable, except for postural dizziness. In Foreign Study 2207 (a single dose of 300 mg once daily), the incidence of adverse events was 21.9% (7 of 32 subjects) after fasted administration and 35.5% (11 of 31 subjects) after fed administration. On the other hand, in Japanese Studies 1201 (30 minutes before a meal) and 1301 (the study drug was taken without regard to meals), the incidence of adverse events in the aliskiren 150 mg group was 51.8% (58 of 112 subjects) and 50.3% (152 of 302 subjects), respectively, and the nature of adverse events was also similar. There were no differences according to whether the timing of dosing relative to meals was specified or not.

As described in the above, even when the exposure to aliskiren was changed due to food effect, there were no findings that raise a safety concern. Thus, it is unnecessary to recommend taking aliskiren after a meal in the Dosage and Administration section of the package insert.

From an efficacy point of view, PMDA asked the applicant to explain the potential for variability in plasma concentration due to food effect to affect the antihypertensive effect of aliskiren and then provide the reason for considering that an additional effect can be obtained appropriately by increasing the dose from 150 mg to 300 mg without instructions for the timing of dosing relative to meals.

The applicant responded as follows:

In Japanese Study 1101, following single doses of 75 to 600 mg of aliskiren, PRA was inhibited with

increasing doses of aliskiren. In Foreign Study 2202, maximal inhibition of PRA was reached within 1 hour of administration of 300 mg of aliskiren in most subjects (Japanese). While PRA after a single dose tended to return to baseline levels at 24 hours post-dose, PRA after repeated administration remained low, suggesting persistent inhibition of renin activity regardless of plasma aliskiren concentration from trough to peak (C_{max}) after plasma aliskiren concentrations reach a steady-state. The correlation between the antihypertensive effect and PRA was significant at ≥ 150 mg ($P \leq 0.01$) and the significance of the association between changes in PRA and the antihypertensive effect tended to increase with increasing dose. Although the degree of inhibition of renin activity differs depending on dose, a decrease in the exposure to aliskiren after fed administration is unlikely to significantly affect the inhibition of renin activity at a steady-state where renin activity is persistently inhibited, and therefore the antihypertensive effect should be maintained. While Japanese Studies 1201 (30 minutes before a meal) and 1301 (the study drug was taken without regard to meals) are placebo-controlled studies conducted under different conditions as to the timing of dosing relative to meals, the difference in the change in mean sitting diastolic blood pressure (msDBP) between the aliskiren 150 mg and placebo groups was comparable for these two studies. On the other hand, an additional effect after forced titration from 150 mg to 300 mg and the antihypertensive effect after optional titration to 300 mg if the effect of 150 mg is insufficient have been shown in Japanese and foreign clinical studies. Meanwhile, it is more preferable to avoid a large variability in the exposure by complying with the same pattern for taking aliskiren with regard to meals each day (before or after a meal). Therefore, referring to the wording in the US labeling, it has been stated in the Precautions in Use section of the proposed package insert that “since the pharmacokinetics of aliskiren is affected by food, patients should be advised to establish a routine pattern for taking aliskiren with regard to meals.”

PMDA considers as follows:

Because of variability in the exposure due to food effect, the usual dose of 150 mg may be equivalent to or higher than the maximum dose of 300 mg in terms of exposure and 300 mg may result in a higher exposure than 600 mg, which is the dose that has been tolerated, but has been associated with a markedly higher incidence of gastrointestinal symptoms overseas according to the applicant’s explanation. Since the BA of aliskiren is as very low as about 2%, the influences of the sources of BA variability on plasma aliskiren concentration and large intra- and inter-individual variability of plasma aliskiren concentration can be easily anticipated. Therefore, there is a limitation to the evaluation of the food effect on the exposure of aliskiren based only on comparison of the mean values obtained from studies. Also, considering that the exposure variability due to food effect in individual patients is larger than the range of exposures with the proposed dosage regimen of aliskiren, a cautious stance should be taken to conclude that food has no effect on the efficacy and safety of aliskiren. In view of the characteristics of the pharmacokinetics of aliskiren, essentially, the timing of dosing relative to meals in a confirmatory study should have been specified based on the results of food effect studies before the conduct of a confirmatory study. Consequently, since the study drug was administered without regard to meals in the confirmatory study, it is difficult to limit the timing of taking aliskiren to either after or before a meal and if aliskiren is taken without regard to meals, steady gastrointestinal absorption cannot be achieved, which may be a disadvantage to patients. On the

other hand, in the treatment of hypertension, since the appropriateness of the use of aliskiren and the efficacy and safety of aliskiren will be determined for each patient, monitoring blood pressure over time etc., no instructions for the timing of dosing relative to meals in the Dosage and Administration section will not pose a major problem affecting the approval decision. However, a fixed relation of administration to meals for each patient is certainly preferable and the caution statement proposed by the applicant is critical information that should be included in the Precautions of Dosage and Administration section, instead of the Precautions in Use section. Moreover, as aliskiren is a drug that needs to be taken each day regularly over a long period of time, regardless of the timing of meals, a caution about changing the timing of taking aliskiren relative to meals should also be included in the appropriate section of the package insert. A final decision on the appropriateness of the above conclusion and the details of the caution statements will be made, taking account of comments raised in the Expert Discussion.

4.(ii) Summary of human pharmacokinetic and clinical pharmacology studies

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

4.(ii).A.(1) *In vitro* studies using human biomaterials

4.(ii).A.(1).1) Plasma protein binding and distribution in blood cells (Attached document 4.2.2.3-3)

In an *in vitro* study using human plasma, the extent of binding of aliskiren to plasma protein was concentration-independent over the concentration range of 10, 50, 250, and 500 ng/mL of ^{14}C-aliskiren (0.018-0.91 µmol/L) and was 49% to 53%. The fraction unbound in human serum was about 37%. In an *in vitro* study using human blood, ^{14}C-aliskiren was incubated at 37°C for 1 hour at concentrations of 10, 50, 250, and 500 ng/mL. The blood to plasma concentration ratio (blood/plasma) was concentration-independent and was ranging from 68% to 75%.

4.(ii).A.(1).2) *In vitro* metabolism in human liver

(a) Metabolism of aliskiren (Attached document 4.2.2.4-2, -3)

Human cytochrome P450 (CYP) isoenzymes involved in the oxidative metabolism of aliskiren were investigated using human liver microsomes and recombinant human CYP. When ^{3}H-aliskiren 1.0, 10, and 100 µmol/L was incubated with human liver microsomes containing NADPH generating system, 8.0%, 11.8%, and 40.0%, respectively, of aliskiren remained unchanged at 60 minutes. Five different metabolites, M1, M2, M3, M4, and M8, were identified. The apparent Michaelis constant (K_m) and maximum velocity (V_{max}) were 43.8 µmol/L and 1807.6 pmol/min/mg, respectively, and the intrinsic clearance of hepatic metabolism (apparent hepatic intrinsic clearance) was 41.3 µL/mg/min. Aliskiren was mainly metabolized by recombinant human CYP3A4 and CYP2D6 and to a minor extent by CYP3A5. The metabolism of aliskiren in human liver microsomes was almost completely inhibited by ketoconazole and also by troleandromycin. A monoclonal antibody specific to CYP3A4 produced 90% inhibition of the human liver microsomal metabolism of aliskiren and taking also account of the CYP abundance values, CYP3A4/5 contributes predominantly (99.6%) to the oxidative metabolism of aliskiren in human liver microsomes.

(b) Drug interactions (Attached document 4.2.2.6-1, -2)

In an *in vitro* study using human liver microsomes, CYP inhibition by aliskiren was investigated in detail. When aliskiren was added at concentrations up to 200 µmol/L to each of the specific substrates for CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1, the metabolism was inhibited by up to 43% and IC_{50} values could not be calculated. The percent inhibition of CYP3A4/5-mediated metabolism differed, depending on the substrate tested (IC_{50} values were 251 µmol/L for the hydroxylation of midazolam and 71 µmol/L for the hydroxylation of testosterone). The maximum plasma concentration at steady-state following repeated oral administration of 300 mg/day of aliskiren (C_{max}^{ss}) was roughly < 2 µmol/L and aliskiren is unlikely to inhibit the CYP-mediated metabolism of co-administered drugs.

4.(ii).A.(1).3) Drug interactions mediated by transporters (Attached document 4.2.2.7-1 - 5)

In transport studies using Caco-2 cells, transport of aliskiren (1 µmol/L) was not inhibited by the addition of a P-glycoprotein (MDR1) inhibitor, verapamil (100 µmol/L), but was inhibited by the addition of potent P-glycoprotein inhibitors, PSC833 (0.2-2 µmol/L) and cyclosporine A (10 µmol/L). Purified membrane vesicles from recombinant baculovirus-infected Sf9 cells or mammalian cell line expressing MDR1 (human multidrug resistance protein 1), MRP2 (human multidrug resistance-associated protein 2) or MXR (mitoxantrone resistance protein) were incubated with aliskiren 0.04 to 98.0 µmol/L and ATPase activity was measured. Aliskiren was shown to stimulate MDR1-ATPase activity at low concentrations (K_m value = 2 µmol/L). Aliskiren did not stimulate MRP2-ATPase or MXR-ATPase activity. The above results indicate that aliskiren is a substrate for the efflux transporter P-glycoprotein.

An investigation using human hepatocytes showed that passive diffusion and active transport are involved in the uptake of aliskiren into hepatocytes, but active transport is predominant and the apparent K_m value for active uptake was 34 µmol/L. Increased uptake of aliskiren into recombinant human organic anion transporter hOATP1-expressing *Xenopus laevis* oocytes was observed, and the apparent K_m value (170 µmol/L) was 5-fold higher than that for human hepatocytes. However, in a study using CHO cells stably transfected with human organic cation transporter hOCT1 or hOCT3, uptake of aliskiren was not observed. When the inhibition of the uptake of 1-methyl-4-phenylpyridinium (MPP), a model substrate for hOCT1, was measured within the concentration range of 0.00001 to 100 µmol/L of ^{14}C-aliskiren, the apparent inhibition constant (K_i value) was 93 µmol/L.

4.(ii).A.(2) Pharmacokinetics in healthy adult volunteers

4.(ii).A.(2).1) Single-dose studies

(a) Japanese single-dose study (Attached document 5.3.3.1-1, Study 1101 [[redacted] to [redacted] 20[redacted]])

Following single oral doses of 75, 150, 300, or 600 mg of aliskiren to 24 Japanese healthy adult male volunteers in the fasted state, peak plasma concentrations of aliskiren were reached at 0.5 to 6.0 hours post-dose (the median values in the aliskiren groups were 0.5-1.5 hours). The C_{max} values in the aliskiren 75, 150, 300, and 600 mg groups were 34.9 ± 19.2 (mean ± SD), 83.7 ± 71.4, 150 ± 67, and 384 ± 148 ng/mL, respectively, the $AUC_{0\text{-}inf}$ values were 225 ± 127, 587 ± 308, 1000 ± 510, and 3720 ± 760 ng·h/mL, respectively, and the $t_{1/2}$ values were 32.5 ± 18.9, 37.0 ± 7.2, 33.5 ± 5.1, and 30.9 ± 4.0 hours, respectively.

The plasma concentration-time curve of aliskiren was biphasic in many subjects. C_{max} and $AUC_{0\text{-}inf}$ increased almost dose-proportionally at doses up to 300 mg, and more than dose-proportional increases in C_{max} and $AUC_{0\text{-}inf}$ were observed at 600 mg. The mean urinary excretion rate of aliskiren was 0.2% to 0.6% and the mean CL_r was 1.02 to 1.40 L/h.

(b) Foreign single-dose study (Attached document 5.3.3.1-2, Study 2205 [[redacted] to [redacted] 20[redacted]], Reference data)

Following single oral doses of 75, 150, 300, and 600 mg of aliskiren to 32 foreign healthy adult male subjects in the fasted state, the $AUC_{0\text{-}t}$ values (arithmetic mean) were 266, 530, 1480, and 3240 ng·h/mL, respectively, and the C_{max} values were 26.3, 72.0, 202, and 420 ng/mL, respectively. The coefficients of variation (CV) for AUC and C_{max} were 55% to 64% and 59% to 117%, respectively, both showing high inter-subject variability. The t_{max} and $t_{1/2}$ values were similar across the doses.

4.(ii).A.(2).2) Multiple-dose study (Attached document 5.3.3.3-4, Study 2202 [[redacted] to [redacted] 20[redacted]])

Nineteen Japanese healthy adult male subjects and 19 Caucasian healthy adult male subjects received a single 300 mg oral dose of aliskiren, underwent a 2-day washout period, and then received multiple (once a day for 7 days) oral doses of 300 mg of aliskiren. The $AUC_{0\text{-}t}$ following a single dose was 1387.0 ± 614.7 ng·h/mL in Japanese and 1123.7 ± 338.5 ng·h/mL in Caucasians and the $AUC_{0\text{-}tau}$ following multiple doses was 2518.6 ± 1175.7 ng·h/mL in Japanese and 2134.6 ± 791.4 ng·h/mL in Caucasians. The C_{max} following a single dose was 214.6 ± 121.6 ng/mL in Japanese and 185.7 ± 91.5 ng/mL in Caucasians and the C_{max} following multiple doses was 403.4 ± 192.8 ng/mL in Japanese and 320.5 ± 188.6 ng/mL in Caucasians. Steady-state was reached after 5 to 7 days in both Japanese and Caucasians and comparison of the AUC and C_{max} values following a single oral dose and multiple oral doses for 7 days indicated an accumulation ratio of approximately 2.

The mean PRA at baseline was slightly lower in Caucasians than in Japanese, which was maintained throughout the administration of aliskiren. In both Japanese and Caucasians, following administration of aliskiren, PRA was reduced rapidly and there was an increase in plasma renin concentration and these parameters showed a tendency to return to baseline at 24 hours post-dose.

4.(ii).A.(2).3) Mass balance study (Attached document 5.3.3.1-3, Study 2223 [[redacted] to [redacted] 20[redacted]], Reference data)

Following a single oral 300 mg dose of ^{14}C-aliskiren to 4 foreign healthy adult male subjects, the median t_{max} values of unchanged aliskiren in plasma and of radioactivity in plasma were both 3 hours, the C_{max} was 253.6 ± 163.0 ng/mL and 305.1 ± 193.3 ng Eq/mL, respectively, the $AUC_{0\text{-}inf}$ was 1107.8 ± 545.8 ng·h/mL and 1373.9 ± 637.8 ng Eq·h/mL, respectively, the initial $t_{1/2}$ ($t_{1/2\lambda 1}$) was 2.15 ± 0.78 and 1.78 ± 0.39 hours, respectively, and the terminal $t_{1/2}$ ($t_{1/2\lambda Z}$) was 48.7 ± 6.88 and 44.3 ± 9.38 hours, respectively, and the plasma concentration-time curves of the unchanged drug and radioactivity were approximately parallel. Approximately 81% of the $AUC_{0\text{-}inf}$ of plasma radioactivity was due to unchanged aliskiren (approximately 86% of $AUC_{0\text{-}10h}$).

The main metabolic pathways of aliskiren appeared to be oxidation at the phenol moiety and the attached side chain by *O*-demethylation, *O*-dealkylation or alcohol oxidation. M1, M2, and M3 were detected in plasma and M4 and a glucuronide conjugate of M4, i.e. M6 were detected in urine. At t_{max}, M2 levels were ≤ 1% of unchanged aliskiren and levels of M3 were in a range of 1% to 5% of unchanged aliskiren.

Unchanged aliskiren was the predominant compound in the urine and feces. The cumulative excretion of radioactivity up to 168 hours post-dose (mean) was approximately 0.6% in urine and approximately 91% in feces. The total urinary and fecal recovery was approximately 92% of the dose. Most of the fecal radioactivity was considered to be attributable to unchanged aliskiren excreted unabsorbed and based on the total urinary radioactivity (0.6% of the radioactive dose) and fecal metabolites (2%-3% of the radioactive dose), the absorption rate was estimated to be ≥ 3% of the dose administered.

4.(ii).A.(3) Pharmacokinetics/pharmacodynamics in patients

4.(ii).A.(3).1) Study to evaluate the pharmacokinetics, pharmacodynamics, and antihypertensive effect of aliskiren in Japanese patients with essential hypertension (Attached document 5.3.4.2-1, Study 1104 [January to [redacted] 2007])

Thirty-three Japanese patients with essential hypertension received multiple oral doses of 150 and 300 mg of aliskiren once daily at 30 minutes after breakfast for 4 weeks. The C_{max} was 30.5 ± 38.2 and 97.2 ± 132 ng/mL, respectively, on the starting day of treatment and 22.9 ± 17.0 and 91.8 ± 96.6 ng/mL, respectively, on the last day of treatment. The AUC_{0-t} was 113 ± 98.7 and 355 ± 371 ng·h/mL, respectively, on the starting day of treatment and 226 ± 136 and 679 ± 379 ng·h/mL, respectively, on the last day of treatment. The trough plasma aliskiren concentration at 24 hours after the last dose was 6.98 ± 4.76 ng/mL at 150 mg and 18.9 ± 10.5 ng/mL at 300 mg. Following multiple oral doses of 150 and 300 mg of aliskiren once daily for 4 weeks in the fed state, the AUC_{0-t} on the last day of treatment was approximately 2-fold higher than the AUC_{0-t} on the starting day of treatment. The trough plasma aliskiren concentrations at 150 and 300 mg on the last day of treatment were 3.8-fold and 4.6-fold, respectively, higher than those on the start day of treatment.

The mean PRA on the starting day of treatment, in both aliskiren groups, rapidly declined immediately after administration of aliskiren and reached the minimum level at 1 hour post-dose and then returned to baseline. The mean PRA on the last day of treatment, in both aliskiren groups, gradually declined after administration of aliskiren and reached the minimum level at 1 hour post-dose and then remained lower than baseline throughout the day. The difference of the area under the effect-time curve between baseline and the treatment (ΔAUE) for PRA on the last day of treatment was 8.56 ± 9.69 ng/mL (mean ± SD) in the aliskiren 150 mg group and 8.88 ± 4.88 ng/mL in the aliskiren 300 mg group. There were no major differences between the two groups.

The mean plasma Ang I, Ang II, and aldosterone concentrations on the starting day of treatment, in both aliskiren groups, were decreased after administration and then remained lower than baseline throughout the

day. On the last day of treatment, these levels remained almost unchanged throughout the day. The mean plasma renin concentration, in both aliskiren groups, rapidly increased immediately after administration on the starting day of treatment. On the last day of treatment, it remained higher than baseline throughout the day.

The mean supine DBP and the mean supine SBP, in both aliskiren groups, were reduced after administration of aliskiren and remained lower than baseline throughout the day on both the starting day and last day of treatment. On the last day of treatment, the mean ΔAUE and the mean maximal change from time-matched baseline value (ΔE_{max}) for the mean supine DBP were 86.9 and 11.2 mmHg, respectively, in the aliskiren 150 mg group and 118 and 12.3 mmHg, respectively, in the aliskiren 300 mg group and the mean ΔAUE and the mean ΔE_{max} for the mean supine SBP were 76.0 and 15.0 mmHg, respectively, in the aliskiren 150 mg group and 183 and 16.2 mmHg, respectively, in the aliskiren 300 mg group.

4.(ii).A.(3).2) Pharmacokinetic evaluation in Japanese patients with essential hypertension (Attached document 5.3.5.1-2, Study 1301 [20 to 20])

Aliskiren 150 mg was orally administered once daily (without regard to meals) for 8 weeks to 302 Japanese patients with essential hypertension. The trough plasma aliskiren concentrations at Treatment Week 4 and Treatment Week 8 were 8.35 ± 10.4 (298 subjects) and 8.71 ± 10.7 ng/mL (289 subjects), respectively.

PRA was remeasured by high sensitivity PRA assay (hsPRA assay) after unblinding, because the time course/changes of mean PRA measured by an assay that is commonly used in Japanese clinical practice (the usual assay method) were not consistent with the results obtained from previous studies in hypertensive patients. Although the results in the placebo and losartan 50 mg groups were similar between the two assay methods, the results were different in the aliskiren 150 mg group, depending on the assay method. Namely, the percent change in PRA (the usual assay method) from baseline to Treatment Week 8 was 7.5% in the aliskiren 150 mg group and 136.7% in the losartan 50 mg group, i.e., PRA was increased in these groups while PRA was reduced by 4.9% in the placebo group. The percent change in PRA (hsPRA assay) from baseline to Treatment Week 8 was -84.5% in the aliskiren 150 mg group while PRA was increased by 26.2% in the losartan 50 mg group and by 10.1% in the placebo group.

The plasma aldosterone concentration was increased by 10.6% from baseline at Treatment Week 8 in the losartan 50 mg group while it was decreased by 9.9% in the aliskiren 150 mg group and by 2.2% in the placebo group. The percent change in plasma renin concentration from baseline to Treatment Week 8 was 338.5% in the aliskiren 150 mg group and 92.2% in the losartan 50 mg group, showing increases in plasma renin concentrations in both of these groups, while there was a 10.2% reduction in the placebo group. The plasma Ang II concentration was increased by 0.7% from baseline at Treatment Week 8 in the aliskiren 150 mg group and by 19.0% in the losartan 50 mg group while it was decreased by 10.5% in the placebo group.

4.(ii).A.(3).3) Pharmacokinetic evaluation in Japanese hypertensive patients with renal impairment (Attached document 5.3.5.2-2, Study 1303 [20 to 20])

Forty Japanese hypertensive patients with renal impairment (serum creatinine, ≥ 1.3 mg/dL and < 3.0 mg/mL for men, ≥ 1.2 mg/dL and < 3.0 mg/mL for women) received a starting dose of 75 mg of aliskiren and the dose was up-titrated at intervals of 2 weeks to 150 mg and then to 300 mg in a stepwise manner according to blood pressure values. Aliskiren was orally administered once daily for 8 weeks and trough plasma aliskiren concentrations were measured. The trough plasma aliskiren concentration in the patients on 75 mg at Treatment Weeks 2, 4, and 8 was 7.74 ± 12.2 (n = 39) , 6.15 ± 5.71 (n = 11), and 5.31 ± 2.83 ng/mL (n = 9), respectively, the trough plasma aliskiren concentration in the patients on 150 mg at Treatment Weeks 4 and 8 was 14.2 ± 10.2 (n = 26) and 20.3 ± 11.9 ng/mL (n = 4), respectively, and the trough plasma aliskiren concentration in the patients on 300 mg at Treatment Week 8 was 34.8 ± 23.6 ng/mL (n = 27). Based on the relationship between creatinine clearance (CCr) and dose-normalized trough plasma aliskiren concentration, trough plasma aliskiren concentrations tended to increase with decreasing creatinine clearance.

4.(ii).A.(4) Pharmacokinetics in special populations

4.(ii).A.(4).1) Comparison between foreign elderly and non-elderly subjects (Attached document 5.3.3.3-1, Study 2217 [to 20])

Following a single oral dose of 300 mg of aliskiren to 28 non-elderly (18-45 years of age) and 29 elderly (65-74 years, n = 16; ≥ 75 years, n = 13) foreign subjects after a 10-hour fast, the median t_{max} values in the 18-45 year-old group, the 65-74 year-old group, and the ≥ 75 year-old group were 2.0, 2.0, and 1.5 hours, respectively, the C_{max} values were 374.5 ± 290.8, 451.8 ± 407.4, and 604.1 ± 605.4 ng/mL, respectively, the AUC_{0-t} values were 1560 ± 977, 2410 ± 1675, and 2611 ± 1910 ng·h/mL, respectively, and the $t_{1/2}$ values were 60.6 ± 15.9, 69.6 ± 12.5, and 69.7 ± 11.4 hours, respectively.

4.(ii).A.(4).2) Foreign patients with chronic hepatic impairment in comparison with healthy controls (Attached document 5.3.3.3-2, Study 2210 [to 20])

The pharmacokinetics following a single oral dose of 300 mg of aliskiren in 18 foreign healthy adult subjects and 18 patients with mild (Child-Pugh Clinical Assessment score, 5-6), moderate (score, 7-9), or severe (score, 10-15) chronic hepatic impairment (6 patients per group) after a 10-hour fast, was determined. The healthy control group for each of the three groups of patients with hepatic impairment was matched by gender, race, age, and body weight. The median t_{max} in matched healthy control subjects and patients with hepatic impairment was 0.5 and 0.5 hours, respectively, for mild impairment, 1.0 and 0.8 hours, respectively, for moderate impairment, and 3.0 and 0.5 hours, respectively, for severe impairment, and the plasma aliskiren concentration-time curve was biphasic in healthy adult subjects that are matched to patients with severe hepatic impairment. The C_{max} was 258.2 ± 133.8 and 267.0 ± 111.3 ng/mL, respectively, for mild impairment, 190.4 ± 97.4 and 291.6 ± 252.0 ng/mL, respectively, for moderate impairment, and 220.7 ± 174.2 and 222.8 ± 121.2 ng/mL, respectively, for severe impairment. The AUC_{0-t} was 1349 ± 600 and 1438 ± 1166 ng·h/mL, respectively, for mild impairment, 1203 ± 323 and 1506 ± 944

ng·h/mL, respectively, for moderate impairment, and 1336 ± 588 and 1371 ± 356 ng·h/mL, respectively, for severe impairment, and the $t_{1/2}$ was 46.6 ± 11.4 and 52.2 ± 11.5 hours, respectively, for mild impairment, 48.4 ± 10.1 and 64.9 ± 12.0 hours, respectively, for moderate impairment, and 57.9 ± 2.7 and 86.1 ± 18.5 hours, respectively, for severe impairment.

4.(ii).A.(4).3) Foreign patients with renal impairment in comparison with healthy controls (Attached document 5.3.3.3-3, Study 2209 [20 to 20])

The pharmacokinetics following multiple oral doses of 300 mg of aliskiren once daily for 7 days in 18 foreign healthy adult subjects and 18 patients with mild (CCr, 50-80 mL/min), moderate (30-49 mL/min), or severe (< 30 mL/min) renal impairment (6 patients per group) after a 10-hour fast, was determined. Healthy adult subjects were matched with each of the three groups of patients with renal impairment by gender, race, age, and body weight. After multiple dosing, the median t_{max}^{ss} in matched healthy control subjects and patients with renal impairment was 2.50 and 1.00 hours, respectively, for mild impairment, 1.00 and 0.50 hours, respectively, for moderate impairment, and 1.00 and 1.52 hours, respectively, for severe impairment. The C_{max}^{ss} was 204.2 ± 93.9 and 545.7 ± 430.2 ng/mL, respectively, for mild impairment, 197.6 ± 46.9 and 350.4 ± 281.0 ng/mL, respectively, for moderate impairment, and 342.6 ± 381.3 and 200.1 ± 137.9 ng/mL, respectively, for severe impairment. The C_{min}^{ss} was 17.2 ± 7.2 and 36.1 ± 33.5 ng/mL, respectively, for mild impairment, 20.0 ± 5.8 and 39.0 ± 13.3 ng/mL, respectively, for moderate impairment, and 15.9 ± 7.8 and 34.1 ± 16.0 ng/mL, respectively, for severe impairment. The $AUC_{0\text{-}tau}$ was 1109.4 ± 477.3 and 2799.0 ± 2459.8 ng·h/mL, respectively, for mild impairment, 1165.8 ± 166.9 and 2449.3 ± 1742.4 ng·h/mL, respectively, for moderate impairment, and 1575.7 ± 1261.5 and 1689.9 ± 1015.5 ng·h/mL, respectively, for severe impairment. Although the exposure tended to increase in patients with renal impairment compared to healthy adult subjects, the increase did not correlate with the severity of renal impairment. The mean accumulation ratio after multiple dosing was 1.3 to 2.2 in healthy adult subjects and 1.3 to 1.6 in patients with renal impairment.

4.(ii).A.(5) Drug interactions

4.(ii).A.(5).1) Drug interaction studies with potentially co-administered drugs

(a) Valsartan (Attached document 5.3.3.4 -4, Study 2216 [20], Reference data)

After a 10-hour fast, 19 foreign healthy adult subjects were orally administered valsartan 320 mg once daily (4 days) followed by 3 days of washout then aliskiren 300 mg once daily (7 days) followed by aliskiren 300 mg plus valsartan 320 mg once daily (4 days). When aliskiren was co-administered with valsartan, the $AUC_{0\text{-}tau}$ and C_{max}^{ss} of aliskiren were reduced by 26% and 28%, respectively, compared with aliskiren administered alone. Also, when valsartan was co-administered with aliskiren, the $AUC_{0\text{-}tau}$ and C_{max}^{ss} of valsartan were reduced by 14% and 12%, respectively, compared with valsartan administered alone. PRA was decreased following the administration of aliskiren alone while it was increased following the administration of valsartan alone and the increase in PRA with valsartan alone was reduced when co-administered with aliskiren. The reduction in plasma aldosterone levels tended to be slightly greater following combination treatment than that following either valsartan or aliskiren alone. Plasma renin levels were higher than the normal range (2.4-29 mU/L) with all treatments. The maximum plasma renin levels

following the administration of aliskiren and of valsartan were 1130 ± 1120 mU/L (mean ± SD) and 1160 ± 1070 mU/L, respectively. The renin level at 6 hours after the co-administration of aliskiren and valsartan was approximately 3-fold higher than that after the administration of either aliskiren or valsartan alone (maximum plasma renin level, 3130 ± 1550 mU/L). In healthy subjects, SBP was lower during combination treatment compared with either monotherapy.

(b) Irbesartan (Attached document 5.3.3.3-3, Study 2209 [20 to 20])

After a 10-hour fast, 11 foreign patients with renal impairment (6 patients with mild renal impairment, 5 patients with moderate renal impairment) and 11 healthy adult male subjects were orally administered aliskiren 300 mg once daily (7 days) and then co-administered aliskiren 300 mg plus irbesartan 300 mg once daily (7 days). When aliskiren was co-administered with irbesartan, the $AUC_{0\text{-}tau}$ and C_{max}^{ss} of aliskiren were reduced by 7% and 33%, respectively, in patients with renal impairment and by 18% and 27%, respectively, in healthy adult subjects, compared with aliskiren administered alone.

(c) Amlodipine (Attached document 5.3.3.4-5, Study 2218 [to 20], Reference data)

After a 10-hour fast, 25 foreign healthy adult subjects were orally administered amlodipine 10 mg once daily (14 days) followed by 7 days of washout then aliskiren 300 mg once daily (14 days) followed by aliskiren 300 mg plus amlodipine 10 mg once daily (14 days). When aliskiren was co-administered with amlodipine, the $AUC_{0\text{-}tau}$ and C_{max}^{ss} of aliskiren were increased by 29% and 18%, respectively, compared with aliskiren administered alone. The $AUC_{0\text{-}tau}$ and C_{max}^{ss} of amlodipine administered in combination with aliskiren were similar to those of amlodipine monotherapy.

(d) Hydrochlorothiazide (Attached document 5.3.3.4-9, Study 2228 [20], Reference data)

After a 10-hour fast, 22 foreign healthy adult subjects were orally administered hydrochlorothiazide (HCTZ) 25 mg once daily (4 days) followed by 4 days of washout then aliskiren 300 mg once daily (7 days) followed by aliskiren 300 mg plus HCTZ 25 mg once daily (4 days). When aliskiren was co-administered with HCTZ, the $AUC_{0\text{-}tau}$ and C_{max}^{ss} of aliskiren were decreased by 7% and 22%, respectively, compared with aliskiren administered alone. Also, when HCTZ was co-administered with aliskiren, the $AUC_{0\text{-}tau}$ and C_{max}^{ss} of HCTZ were decreased by 10% and 26%, respectively, compared with HCTZ administered alone.

(e) Furosemide (Attached document 5.3.3.4-2, Study 2211 [20], Reference data)

After a 10-hour fast, 21 foreign healthy adult subjects were orally administered furosemide 20 mg once daily (3 days) followed by 3 days of washout then aliskiren 300 mg once daily (7 days) followed by aliskiren 300 mg plus furosemide 20 mg once daily (3 days). Furosemide co-administration decreased the $AUC_{0\text{-}tau}$ and C_{max}^{ss} of aliskiren by 7% and 20%, respectively, and aliskiren co-administration reduced the $AUC_{0\text{-}tau}$ and C_{max}^{ss} of furosemide by 28% and 49%, respectively.

(f) Warfarin (Attached document 5.3.3.4-18, Study 0019 [to 20], Reference data)

Fifteen foreign healthy adult subjects were orally administered 150 mg of aliskiren (Speedel capsule) or placebo once daily (11 days). On Day 8, subjects were orally administered 25 mg of warfarin (5-mg tablet × 5). Trough plasma aliskiren concentrations from Day 6 to Day 11 were almost constant within the range of 8.0 to 11.6 ng/mL (median). When warfarin was co-administered with aliskiren, the $AUC_{0\text{-last}}$ of (*S*)-warfarin was increased by 4% and the C_{max} of (*S*)-warfarin was reduced by 12% compared with warfarin administered alone. The $AUC_{0\text{-last}}$ of (*R*)-warfarin was not affected while the C_{max} of (*R*)-warfarin was decreased by 11%. The 90% confidence interval of the ratio of least squares means of the area under the prothrombin time (PTT)-time curve (estimated using a linear mixed effect model with treatment as a fixed factor and subject as a random factor) for warfarin given in combination with aliskiren to that for warfarin given alone was 0.93 to 1.00, and the 90% confidence interval of the ratio of least squares means of the area under the international normalized ratio for prothrombin time (PT-INR)-time curve for warfarin given in combination with aliskiren to that for warfarin given alone was 0.93 to 1.00.

In addition to the above-mentioned drugs, drug interaction studies of aliskiren with pioglitazone, isosorbide mononitrate, atenolol, fenofibrate, and allopurinol were also conducted. Co-administration of aliskiren with these drugs had little effect on the pharmacokinetic parameters (AUC and C_{max}^{ss}) of either aliskiren or the co-administered drug.

4.(ii).A.(5).2) Drug interaction studies with drugs affecting P-glycoprotein or CYP metabolism

(a) Cyclosporine (Attached document 5.3.3.4-21, Study 2106 [to 20], Reference data)

After a 10-hour fast, foreign healthy adult subjects were orally administered aliskiren 75 mg once daily (5 days, 14 subjects) followed by 7 days of washout then aliskiren 75 mg plus cyclosporine 200 mg once daily (5 days, 13 subjects) followed by 14 days of washout then aliskiren 75 mg plus cyclosporine 600 mg (8 subjects). When aliskiren was co-administered with cyclosporine 200 mg, the $AUC_{0\text{-inf}}$ and C_{max}^{ss} of aliskiren were increased by 328% and 149%, respectively, compared with aliskiren administered alone. Moreover, co-administration of cyclosporine 600 mg increased the $AUC_{0\text{-inf}}$ and C_{max}^{ss} of aliskiren by 399% and 148%, respectively, compared with aliskiren administered alone. When aliskiren was co-administered with cyclosporine, the $t_{1/2}$ and t_{max} of aliskiren were prolonged, compared with aliskiren administered alone.

(b) Atorvastatin (Attached document 5.3.3.4-14, Study 2234 [to 20], Reference data)

After a 10-hour fast, 21 foreign healthy adult subjects were orally administered atorvastatin 80 mg once daily (4 days) followed by 3 days of washout then aliskiren 300 mg once daily (7 days) followed by aliskiren 300 mg plus atorvastatin 80 mg once daily (4 days). When aliskiren was co-administered with atorvastatin, the $AUC_{0\text{-t}}$ and C_{max}^{ss} of aliskiren were increased by 47% and 50%, respectively, compared with aliskiren administered alone. Also, when atorvastatin was co-administered with aliskiren, the $AUC_{0\text{-t}}$ and C_{max}^{ss} of atorvastatin and its active metabolite were decreased by 9% to 11% and 10% to 23%, respectively, compared with atorvastatin administered alone.

(c) Ketoconazole (Attached document 5.3.3.4-17, Study 2334 [20], Reference data)

After a 12-hour fast, 21 foreign healthy adult subjects were orally administered aliskiren 300 mg once daily (7 days) followed by aliskiren 300 mg once daily in the morning plus ketoconazole 200 mg once daily in the evening (Q 12 hours) (4 days). When aliskiren was co-administered with ketoconazole, the $AUC_{0\text{-}tau}$ and C_{max}^{ss} of aliskiren were increased by 76% and 81%, respectively, compared with aliskiren administered alone.

(d) Digoxin (Attached document 5.3.3.4-3, Study 2214 [20 to 20], Reference data)

After a 10-hour fast, 21 foreign healthy adult subjects were orally administered aliskiren 300 mg once daily (7 days) followed by 10 days of washout then digoxin 0.25 mg once daily (9 days) followed by aliskiren 300 mg plus digoxin 0.25 mg once daily (7 days). When aliskiren was co-administered with digoxin, the $AUC_{0\text{-}tau}$ and C_{max}^{ss} of aliskiren were increased by 2% and decreased by 2%, respectively, compared with aliskiren administered alone. Also, when digoxin was co-administered with aliskiren, the $AUC_{0\text{-}tau}$ and C_{max}^{ss} of digoxin were decreased by 15% and 9%, respectively, compared with digoxin administered alone.

(e) Metformin (Attached document 5.3.3.4-6, Study 2220 [20 to 20], Reference data)

After a 10-hour fast, 21 foreign healthy adult subjects were orally administered metformin 1000 mg once daily (4 days) followed by 4 days of washout then aliskiren 300 mg once daily (7 days) followed by aliskiren 300 mg plus metformin 1000 mg once daily (4 days). When aliskiren was co-administered with metformin, the $AUC_{0\text{-}tau}$ and C_{max}^{ss} of aliskiren were reduced by 27% and 29%, respectively, compared with aliskiren administered alone. Also, when metformin was co-administered with aliskiren, the $AUC_{0\text{-}tau}$ and C_{max}^{ss} of metformin were reduced by 12% and 11%, respectively, compared with metformin administered alone.

(f) Cimetidine (Attached document 5.3.3.4-16, Study 2236 [to 20 , Reference data)

After a 10-hour fast, 22 foreign healthy adult subjects were orally administered aliskiren 300 mg once daily (7 days) followed by aliskiren 300 mg plus cimetidine 800 mg once daily (5 days). When aliskiren was co-administered with cimetidine, the $AUC_{0\text{-}tau}$ and C_{max}^{ss} of aliskiren were increased by 20% and 25%, respectively, compared with aliskiren administered alone.

In addition to the above-mentioned drugs, a drug interaction study of aliskiren with celecoxib was also conducted. Co-administration of aliskiren with celecoxib had little effect on the pharmacokinetic parameters (AUC and C_{max}^{ss}) of either aliskiren or celecoxib.

4.(ii).A.(6) Other studies

4.(ii).A.(6).1) Determination of gastrointestinal aliskiren concentrations in foreign healthy subjects (Attached document 5.3.3.1-4, Study 2105 [20], Reference data)

Because changes associated with the local irritant effects of aliskiren observed in non-clinical studies have suggested that high-dose aliskiren produces gastrointestinal toxicity, aliskiren concentrations in feces,

rectal mucosal biopsy samples, and plasma at steady-state after treatment with aliskiren were quantified. Aliskiren 300 mg was orally administered once daily for 8 days to 15 foreign healthy adult male or female subjects aged between 21 and 60 with regular bowel movements (patients with uncomplicated mild to moderate hypertension were also allowed to be enrolled). The fecal aliskiren concentration was 1530 ± 1320 μg/g (mean ± SD) and the aliskiren concentration in rectal mucosal biopsy samples was 22.2 ± 15.6 μg/g. The plasma trough aliskiren concentration was 24.9 ± 9.8 ng/mL and the plasma aliskiren concentration at the time of sigmoidoscopy was 217 ± 204 ng/mL. Both fecal and rectal mucosal drug concentrations showed high inter-subject variability. While there was no correlation between fecal and plasma aliskiren concentrations or between rectal mucosal and plasma aliskiren concentrations, there was a correlation between aliskiren concentration in rectal mucosal biopsy samples and fecal aliskiren concentration at sigmoidoscopy (n = 7, r = 0.934).

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

4.(ii).B.(1) Pharmacokinetics and pharmacokinetics/pharmacodynamics of aliskiren

The pharmacokinetics of aliskiren is characterized by a very low BA (absolute BA, 1.9%-2.6%), high intra- and inter-individual variability (intra-individual CV, 34%-66%; inter-individual CV, 54%-87%), and more than dose-proportional increases in C_{max} and AUC at 600 mg compared to the dose range of 75 to 300 mg. CYP3A4 is primarily involved in the hepatic metabolism of aliskiren, aliskiren and its metabolites are excreted mainly in bile, and P-glycoprotein is considered to be the major efflux transporter involved in the excretion of aliskiren.

The applicant explained about intra- and inter-individual variability of plasma aliskiren concentration as follows:

High intra- and inter-individual variability is considered attributable to a biphasic plasma aliskiren concentration-time curve and the level of expression of MDR1, a transporter involved in the absorption and excretion of aliskiren, and its activity, etc. It has been reported that the plasma concentrations of tacrolimus, cyclosporine, and digoxin, which are substrates for p-glycoprotein, are correlated with the level of expression of MDR1 or its activity (Masuda S et al. *Clinical Pharmacology & Therapeutics.* 2006;79:90-102, Masuda S et al. *Liver Transpl.* 2003;9:1108-13) and the plasma levels of aliskiren are also considered to be affected by the level of expression of MDR1.

PMDA considers as follows:

It is unknown whether inter-individual variability in the pharmacokinetics of aliskiren is due to inter-individual variability in the level of expression of MDR1. However, since the BA of aliskiren is very low and high intra- and inter-individual variability have been observed, it is important to appropriately advise caution about and provide information on the sources of pharmacokinetic variability in individual patients. Especially, drug interactions will be carefully reviewed in "4.(ii).B.(2) Drug interactions."

In the study to investigate the relationship between pharmacokinetics and pharmacodynamics, following a single dose of aliskiren, PRA changed with changes in plasma concentration, reached the minimum level

at 1 hour post-dose and then returned to baseline, but it remained lower than baseline at steady-state and the AUE and E_{max} for PRA were similar between the aliskiren 150 mg and 300 mg groups. On the other hand, the applicant explained that the correlation between the antihypertensive effect and PRA was significant at ≥ 150 mg and the significance of the association tended to increase with increasing dose and the mean ΔAUE and ΔE_{max} for the mean supine SBP were shown to increase proportionally with increasing dose from 150 mg to 300 mg (Japanese Study 1104).

However, in Japanese Study 1301, when PRA was measured by the usual assay method that was used in a majority of clinical studies, the results in the aliskiren 150 mg group were not consistent with the results obtained from other clinical studies and the applicant explained that PRA was remeasured by hsPRA assay, which showed a similar trend to the previous results. Thus, PMDA asked the applicant to explain the reason for discrepancies in PRA results between these two assays and the appropriateness of comparing PRA remeasured by hsPRA assay with PRA obtained in other clinical studies.

The applicant responded as follows:
In Japanese Study 1301, there was no clear reduction from baseline in PRA when measured by the usual assay method, which was considered attributable to a small number of subjects who had their PRA measured in this study (20 subjects) and high values at the final measuring time in a few subjects. PRA was remeasured in residual plasma samples, but the volumes of these plasma samples were only 25 to 50 μL, which fell short of the volume required for the usual assay method or the antibody trapping method. Thus, hsPRA assay was chosen. Like the usual assay method, hsPRA assay measures the amount of Ang I generated per unit time. However, unlike the usual assay method, hsPRA assay involves the addition of an exogenous substrate (sheep angiotensinogen) and the affinity of this substrate for human renin is higher than that of human angiotensinogen and the amount of generated Ang I is increased with hsPRA assay compared with the usual assay method. Therefore, it is inferred that a reduction in PRA from baseline is more evident with hsPRA assay compared to the usual assay method. Also in Foreign Study 2242, PRA was assessed using the usual assay method and hsPRA assay and following 4-week administration of 300 mg of aliskiren, the geometric mean PRA was reduced from baseline by 67% and 87%, respectively. On the other hand, because the baseline values obtained by hsPRA assay were 20- to 25-fold higher than the baseline values obtained by the usual assay method and there was also no correlation between these measurements, it is not appropriate to directly compare the measurements obtained by the usual assay method with those obtained by hsPRA assay. Meanwhile, in Japanese Study 1301, PRA obtained by hsPRA assay was reduced from baseline in the aliskiren group compared to the losartan control group, which was similar to the results of Foreign Study 2242. Thus, the measurements obtained by hsPRA assay also show that aliskiren inhibited renin activity, as with the results obtained by the usual assay method that was used in Japan and overseas. Although direct comparison of measurements obtained by hsPRA assay with those obtained by the usual assay method is not appropriate, hsPRA assay is another measure of the level of PRA and indicates the degree of inhibition of renin activity by aliskiren.

PMDA considers as follows:
Under the circumstances where changes from baseline in PRA following the administration of aliskiren differ depending on the assay method used, it is difficult to decide which results should be used to evaluate the renin-inhibiting effect of aliskiren and it is hard to say that the relationship between the renin-inhibiting effect and antihypertensive effect of aliskiren has been defined. On the other hand, Japanese and foreign clinical studies have demonstrated the antihypertensive effect of aliskiren and it can be assumed, based on non-clinical study data, that the mode of action of aliskiren involves inhibition of renin activity, resulting in blood pressure reductions. Therefore, even though PRA could not be measured appropriately, it hardly affects the approval decision on its own.

4.(ii).B.(2) Drug interactions

Aliskiren has been found to be a substrate for P-glycoprotein in *in vitro* studies and a drug interaction study in humans (Foreign Study 2106) has shown that the C_{max} and AUC of aliskiren were increased 2.5-fold and 5-fold, respectively, when co-administered with cyclosporine. Taking account of these findings, PMDA asked the applicant to provide a justification for listing cyclosporine in the "Precautions for Concomitant Use" section, instead of the "Contraindications for coadministration" section, in the proposed package insert.

The applicant responded as follows:
In Foreign Study 2106, the C_{max} and AUC of aliskiren were increased when co-administered with cyclosporine, but the incidence of adverse events was 35.7% (5 of 14 subjects) in the aliskiren 75 mg alone group, 69.2% (9 of 13 subjects) in the aliskiren/cyclosporine 75/200 mg co-administration group, and 50.0% (4 of 8 subjects) in the aliskiren/cyclosporine 75/600 mg co-administration group. With respect to the nature of adverse drug reactions, the incidences of somnolence and hot flush were slightly higher with co-administration of aliskiren with cyclosporine compared to aliskiren alone. During the study period, an adverse event rated as severe for which a causal relationship to the study drug could not be denied was 1 case of vomiting in the aliskiren/cyclosporine 75/600 mg co-administration group. Vomiting developed at 1.5 hours after study drug administration and resolved on the day of onset with treatment. According to a report on the administration of aliskiren 150 to 300 mg to 10 heart transplant recipients treated with calcineurin inhibitors (represented by cyclosporine and tacrolimus) (Kittleson MM et al. *J Heart Lung Transplant.* 2008;27:S86-7), 3 of the 10 patients discontinued study medication due to back pain, hypotension, nausea, vomiting, and diarrhoea after 8 weeks, but all events resolved following discontinuation of the study drug. The exposure to aliskiren in patients who receive aliskiren 150 mg plus cyclosporine 200 mg once daily is assumed to be almost equivalent to a 600 mg dose of aliskiren and 600 mg of aliskiren was associated with an increased risk of gastrointestinal adverse drug reactions in foreign clinical studies, but the incidence of diarrhoea rated as severe was comparable in all of the placebo and aliskiren 75, 150, 300, and 600 mg groups. Based on the above, although the exposure of aliskiren is increased when co-administered with cyclosporine, because no serious adverse events that warrant "contraindication of concomitant cyclosporine" have been observed, it has been decided that cyclosporine should be listed in the "Precautions for Concomitant Use" section and that a caution statement that

“concomitant use is not recommended” should be included. The concomitant use of aliskiren with cyclosporine is not contraindicated but is listed in the “PRECAUTIONS” section of the labeling in the US, while the concomitant use of aliskiren with cyclosporine is contraindicated in Europe.

Although PMDA considers that an increase in aliskiren exposure by co-administration of atorvastatin may affect the efficacy and safety of aliskiren, no caution statement about co-administration of atorvastatin is included in the proposed package insert. PMDA asked for the applicant’s view on the necessity of providing a caution or information about the concomitant use of aliskiren with atorvastatin, which is anticipated in clinical practice.

The applicant responded as follows:
In Foreign Study 2234 of drug interactions with atorvastatin, although aliskiren exposure was increased by 50%, a dose that is equivalent to double the highest proposed dose of aliskiren of 300 mg (i.e., 600 mg) is within the dose range investigated in Japanese and foreign clinical studies and the tolerability of 600 mg of aliskiren has been confirmed except for gastrointestinal symptoms. Thus, there should be no safety concerns about a 50% increase in the exposure. In Japanese, short-term, placebo-controlled and short-term controlled studies, the incidence of adverse events among subjects who received concomitant atorvastatin was similar for the placebo group and the aliskiren dose groups except for the aliskiren 300 mg group with a higher incidence and the most common system organ class (SOC) of these adverse events was “infections and infestations.” As of March 31, 2008, aliskiren has already been approved in 44 countries and 1 case of an interaction with atorvastatin has been reported from the marketing experience with aliskiren. In this case, cardiac flutter and extrasystoles due to an interaction with atorvastatin were reported and a causal relationship to aliskiren could not be denied for these events, but this patient concomitantly used multiple drugs (omeprazole, levothyroxine, olmesartan, HCTZ, alprazolam), in addition to atorvastatin. On the other hand, in Japanese and foreign short-term placebo-controlled studies in patients with hypertension, aliskiren demonstrated a superior antihypertensive effect compared to placebo in terms of the change from baseline at Week 8 in msDBP and mean sitting systolic blood pressure (msSBP) in those who received concomitant atorvastatin and co-administration of atorvastatin did not result in excessive blood pressure reductions. Based on the above, co-administration of atorvastatin is very unlikely to affect the safety and efficacy of aliskiren and a caution statement and information about the concomitant use of aliskiren with atorvastatin are unnecessary.

PMDA considers as follows:
Cyclosporine is a P-glycoprotein inhibitor and has been shown to increase the AUC of aliskiren approximately 5-fold in Foreign Study 2106. The usual dose of aliskiren is 150 mg and if a lower dose cannot be chosen [see 4.(iii).B.(2).2).(b) “75 mg (dose reduction as appropriate)”], there is a good possibility that due to a 5-fold variability in the exposure, 150 mg results in a higher exposure than 600 mg that is claimed by the applicant to have been tolerated. In addition, since the applicant has explained that inter-individual variability in the pharmacokinetics of aliskiren is partly attributable to the level of expression of MRD1, co-administration of cyclosporine with aliskiren cannot easily be accepted. Therefore,

taking also into account that multiple antihypertensive agents other than aliskiren are available, the concomitant use of aliskiren with cyclosporine should be contraindicated. Moreover, the proposed package insert submitted by the applicant includes no caution statement about the concomitant use of aliskiren with atorvastatin. Since (1) atorvastatin is another P-glycoprotein inhibitor and the AUC of aliskiren was increased in Foreign Study 2234; (2) if a dose lower than the usual dose cannot be chosen, management, e.g. dose reduction as appropriate, will be difficult; and (3) co-administration of atorvastatin with aliskiren is rather anticipated, it is essential to exercise specific caution and provide information about the concomitant use of aliskiren with atorvastatin, including whether or not co-administration of atorvastatin with aliskiren is acceptable. The European labeling includes a caution about co-administration of atorvastatin and the US labeling states in the PRECAUTIONS section that "patients should report any medications they take with aliskiren." Since aliskiren is a substrate for P-glycoprotein and drug interactions via P-glycoprotein are anticipated to affect absorption into the small intestine and excretion into bile and CYP3A4 is also involved in the hepatic metabolism of aliskiren, though it is impossible to list all drugs requiring caution, it is necessary to exercise specific caution and provide information about at least drugs that will be co-administered with aliskiren commonly in clinical practice and will definitely interact with aliskiren.

The above conclusion by PMDA and specific caution statements in the package insert etc. will be further reviewed taking account of comments from the expert advisors.

4.(iii) Summary of clinical efficacy and safety

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

As the evaluation data, the results from a total of 15 studies (2 biopharmaceutic studies, 5 human pharmacokinetic studies, 1 human pharmacodynamic study, 7 efficacy and safety studies) were submitted. As the reference data, the results from a total of 62 studies (3 biopharmaceutic studies, 25 human pharmacokinetic studies, 2 human pharmacodynamic studies, 18 efficacy and safety studies, 14 other clinical studies) were submitted.

4.(iii).A.(1) Phase I studies

4.(iii).A.(1).1) Food effect study in Japanese healthy adult male subjects (Attached document 5.3.1.1-1, Study 1102 [to 20])

A randomized, open-label, two-treatment, two-period, crossover study (a 10-day washout period) was conducted in 34 Japanese healthy adult male subjects to investigate the effect of the timing of meals on the BA of 150 mg of aliskiren. Adverse events occurred in 14 of 34 fed subjects and 20 of 33 fasted subjects and there were no deaths or serious adverse events. Adverse events occurring in at least 2 fed or fasted subjects include postural dizziness (5 of 34 fed subjects, 10 of 33 fasted subjects), nasopharyngitis (6 of 34 fed subjects, 4 of 33 fasted subjects), orthostatic hypotension (1 of 34 fed subjects, 2 of 33 fasted subjects), dizziness (1 of 34 fed subjects, 2 of 33 fasted subjects), malaise (1 of 34 fed subjects, 2 of 33 fasted subjects), and diarrhoea (2 of 34 fed subjects, 1 of 33 fasted subjects). The incidence of postural dizziness

was higher following fasted administration compared to fed administration [see "4.(i).A.(3).1) Japanese clinical study" for food effect data].

4.(iii).A.(1).2) Single-dose study in Japanese healthy adult male subjects (Attached document 5.3.3.1-1, Study 1101 [to 20])

A single-blind study was conducted in 36 Japanese healthy adult male subjects (12 subjects in the placebo group, 6 subjects in each aliskiren dose group) to evaluate the pharmacokinetics, safety, and pharmacological effects of a single oral dose of aliskiren in the fasted state. Single oral doses of placebo and aliskiren 75, 150, 300, and 600 mg were administered in the fasted state. Adverse events occurred in 0 of 12 subjects in the placebo group, 0 of 6 subjects in the aliskiren 75 mg group, 2 of 6 subjects in the aliskiren 150 mg group, 1 of 6 subjects in the aliskiren 300 mg group, and 2 of 6 subjects in the aliskiren 600 mg group and there were no deaths or serious adverse events. The adverse events reported include postural dizziness (2 of 6 subjects in the aliskiren 150 mg group, 1 of 6 subjects in the aliskiren 600 mg group) and blood pressure decreased (1 of 6 subjects in the aliskiren 150 mg group, 1 of 6 subjects in the aliskiren 300 mg group, 1 of 6 subjects in the aliskiren 600 mg group) [see "4.(ii).A.(2).1).(a) Japanese single-dose study" for pharmacokinetic data].

4.(iii).A.(1).3) Single-dose and multiple-dose study in Japanese and Caucasian healthy adult male subjects (Attached document 5.3.3.3-4, Study 2202 [to 20])

An open-label, parallel-group, comparative study was conducted in 19 Japanese healthy adult male subjects and 19 Caucasian healthy adult male subjects to compare the single and multiple oral dose pharmacokinetics of aliskiren between Japanese and Caucasian healthy adult male subjects. Subjects received a single oral dose of 300 mg of aliskiren, followed by a 2-day washout period, and then received multiple oral doses of 300 mg of aliskiren once daily for 7 days. Adverse events occurred in 8 of 19 Japanese subjects and 13 of 19 Caucasian subjects and there were no deaths or serious adverse events throughout the study period. Adverse events occurring in at least 2 subjects of either ethnic group include headache (3 of 19 Japanese subjects, 7 of 19 Caucasian subjects) and dizziness (4 of 19 Japanese subjects, 3 of 19 Caucasian subjects) [see "4.(ii).A.(2).2) Multiple-dose study" for pharmacokinetic data].

4.(iii).A.(1).4) Pharmacokinetic/pharmacodynamic study in Japanese patients with essential hypertension (Attached document 5.3.4.2-1, Study 1104 [January to 2007])

A randomized, double-blind, parallel-group, comparative study was conducted at 2 centers in Japan to evaluate the pharmacokinetics of aliskiren orally administered at doses of 150 and 300 mg at 30 minutes after the start of breakfast for 28 days (a treatment period) following a run-in period (27-day placebo administration) in Japanese patients with mild to moderate essential hypertension (Target sample size: 34). The main inclusion criteria were as follows: patients aged ≥ 20 and < 80 with essential hypertension; body weight ≥ 50 kg; msDBP at Visit 2 (Day -14) and Visit 3 (Day -3) during the run-in period were "≥ 90 mmHg and < 110 mmHg" and "≥ 95 mmHg and < 110 mmHg," respectively, and the difference in msDBP between Visit 2 and Visit 3 was ≤ 10 mmHg.

All of 33 randomized subjects (16 subjects in the aliskiren 300 mg group, 17 subjects in the aliskiren 150 mg group) completed the study and were included in the safety analysis and the pharmacokinetic/pharmacodynamic analyses.

During the study period, a total of 23 adverse events were observed in 36.4% (12 of 33 subjects) of the Safety Analysis Population. The incidence and number of adverse events by dose level were 29.4% (5 of 17 subjects) and a total of 13 events in the aliskiren 150 mg group and 43.8% (7 of 16 subjects) and a total of 10 events in the aliskiren 300 mg group. There were no adverse events occurring in ≥ 2 subjects in either group. During the study period, there were no deaths or serious adverse events.

During the study period, adverse events judged as clinically relevant were anaemia and thrombocytopenia. Anaemia developed in 1 subject of the aliskiren 300 mg group on Day 29 and resolved 67 days later. A causal relationship of this event to the study drug could not be denied. Thrombocytopenia developed in 1 subject of the aliskiren 150 mg group on Day 29. A causal relationship of this event to the study drug could not be denied on Day 35. Examinations were performed later and as a result, this event was determined to be caused by mild idiopathic thrombocytopenic purpura and a causal relationship to the study drug was denied. This event remained unresolved at the end of the study [see "4.(ii).A.(3).1) Study to evaluate the pharmacokinetics, pharmacodynamics, and antihypertensive effect of aliskiren in Japanese patients with hypertension" for pharmacokinetic/pharmacodynamic data].

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

1) Japanese phase II study (Attached document 5.3.5.1-1, Study 1201 [August 2004 to [redacted] 20[redacted]])

A randomized, double-blind, parallel-group, comparative study in which aliskiren 75, 150, and 300 mg or placebo was orally administered for 8 weeks was conducted at 29 centers in Japan to evaluate the efficacy and dose-response relationship and safety of aliskiren in Japanese patients with mild to moderate essential hypertension (Target sample size: 110 subjects per group, 440 subject in total).

All subjects received placebo during the run-in period (4 weeks) and aliskiren 75, 150, and 300 mg or placebo was orally administered once daily at 30 minutes before breakfast during the treatment period (8 weeks).

The main inclusion criteria were as follows: outpatients with essential hypertension who were aged ≥ 20 and ≤ 80 years at the time of giving consent; and msDBP at Visit 2 (Day -14) and Visit 3 (Day 0) were "≥ 90 mmHg and < 110 mmHg" and "≥ 95 mmHg and < 110 mmHg," respectively, and the difference in msDBP between Visit 2 and Visit 3 was ≤ 10 mmHg. Patients with secondary hypertension or severe hypertension were excluded.

All of 455 randomized subjects (115 subjects in the placebo group, 115 subjects in the aliskiren 75 mg group, 112 subjects in the aliskiren 150 mg group, 113 subjects in the aliskiren 300 mg group) were included in the safety analysis and the Full Analysis Set (FAS) and the FAS was the primary efficacy

analysis population. Of the 455 randomized subjects, 21 subjects (11 subjects, 5 subjects, 3 subjects, and 2 subjects, respectively) prematurely discontinued study medication during the treatment period due to the occurrence of adverse events (10 subjects), consent withdrawal (7 subjects), etc. and 434 subjects completed the study.

The baseline of the study was defined as Day 0 and Week 8 (at the end of the treatment period) was chosen as the primary time point for analysis. Last Observation Carried Forward (LOCF) was used to impute missing data at Week 8.

The primary endpoint of the change from baseline in trough msDBP at Week 8 (LOCF) (Week 8 − Baseline) in the FAS was -3.2 ± 7.8 mmHg (mean ± SD) in the placebo group, -7.2 ± 7.1 mmHg in the aliskiren 75 mg group, -7.7 ± 8.8 mmHg in the aliskiren 150 mg group, and -10.7 ± 8.8 mmHg in the aliskiren 300 mg group. The least squares mean difference between aliskiren and placebo in trough msDBP change from baseline at Week 8 (aliskiren group − placebo group) (95% CI), based on an analysis of covariance (ANCOVA) model including baseline msDBP as a covariate and treatment and region as factors, was -3.96 mmHg (-6.03 to -1.89) in the aliskiren 75 mg group, -4.49 mmHg (-6.57 to -2.41) in the aliskiren 150 mg group, and -7.46 mmHg (-9.54 to -5.38) in the aliskiren 300 mg group and the absolute change in msDBP was significantly greater in all aliskiren groups compared to the placebo group (P = 0.0002, P < 0.0001, and P < 0.0001, respectively, step-down Dunnett's test). The secondary endpoint of the change from baseline in trough msSBP at Week 8 (LOCF) (Week 8 − Baseline) in the FAS was -2.8 ± 12.6 (mean ± SD) in the placebo group, -8.1 ± 12.7 mmHg in the aliskiren 75 mg group, -8.8 ± 12.4 mmHg in the aliskiren 150 mg group, and -14.1 ± 13.7 mmHg in the aliskiren 300 mg group. The least squares mean difference between aliskiren and placebo in trough msSBP change from baseline at Week 8 (aliskiren group − placebo group) (95% CI), based on an ANCOVA model including baseline msSBP as a covariate and treatment and region as factors, was -5.72 mmHg (-8.97 to -2.47) in the aliskiren 75 mg group, -5.87 mmHg (-9.13 to -2.61) in the aliskiren 150 mg group, and -11.2 mmHg (-14.5 to -7.99) in the aliskiren 300 mg group and the absolute change in msSBP was significantly greater in all aliskiren groups compared to the placebo group (P = 0.0006, P = 0.0009, and P < 0.0001, respectively, step-down Dunnett's test).

The incidence of adverse events during the treatment period was similar across all groups including the placebo group, i.e. 50.4% (58 of 115 subjects) in the placebo group, 53.0% (61 of 115 subjects) in the aliskiren 75 mg group, 51.8% (58 of 112 subjects) in the aliskiren 150 mg group, and 54.9% (62 of 113 subjects) in the aliskiren 300 mg group. Adverse events reported by at least 2.0% of subjects in any group are as shown in Table 1.

Table 1. Common adverse events during the treatment period (Adapted from CTD)

Adverse event	Placebo	Aliskiren 75 mg	Aliskiren 150 mg	Aliskiren 300 mg
	N = 115	N = 115	N = 112	N = 113
	n (%)			
Nasopharyngitis	16 (13.9)	24 (20.9)	20 (17.9)	20 (17.7)
ALT increased	3 (2.6)	5 (4.3)	4 (3.6)	2 (1.8)
Headache	4 (3.5)	3 (2.6)	3 (2.7)	6 (5.3)
Blood TG increased	3 (2.6)	3 (2.6)	3 (2.7)	4 (3.5)
Blood CK increased	2 (1.7)	3 (2.6)	0 (0)	1 (0.9)
γ-GTP increased	3 (2.6)	2 (1.7)	1 (0.9)	2 (1.8)
Laryngopharyngitis	3 (2.6)	2 (1.7)	1 (0.9)	1 (0.9)
Blood uric acid increased	0 (0)	2 (1.7)	0 (0)	4 (3.5)
Hyperlipidaemia	2 (1.7)	1 (0.9)	4 (3.6)	0 (0)
Diarrhoea	1 (0.9)	1 (0.9)	1 (0.9)	4 (3.5)
Blood pressure increased	3 (2.6)	1 (0.9)	1 (0.9)	0 (0)
Blood ALP increased	3 (2.6)	0 (0)	0 (0)	2 (1.8)
Arthralgia	3 (2.6)	0 (0)	0 (0)	0 (0)

ALT: alanine aminotransferase, TG: triglyceride, CK: creatine kinase

Serious adverse events (including deaths) occurred in a total of 5 subjects (2 subjects during the run-in period, 3 subjects during the treatment period): One subject in the aliskiren 150 mg group died due to acute drug intoxication during the treatment period, which was determined to be caused by the ingestion of a large amount of a drug other than the study drug and a causal relationship of this death to the study drug was denied. During the run-in period, 1 subject was found to have pancreatic cancer and its metastases to the liver after the discontinuation of placebo, but a causal relationship to the study drug was denied for both events. Other serious adverse events excluding deaths reported during the treatment period were cerebral infarction in 1 subject (placebo group) and acute myocardial infarction in 1 subject (aliskiren 75 mg group) and a causal relationship to the study drug could not be denied for both events. These two subjects had recovered or improved at a follow-up. The remaining 1 subject experienced infectious enterocolitis and dehydration during the run-in period and their causal relationship to the study drug was denied.

Adverse events leading to discontinuation during the treatment period occurred in 10 subjects: 4 subjects in the placebo group (5 events) (arthralgia, blood pressure increased [2 events], cerebral infarction, vertigo), 1 subject in the aliskiren 75 mg group (1 event) (acute myocardial infarction), 3 subjects in the aliskiren 150 mg group (3 events) (drug toxicity, blood pressure increased, hypertension), and 2 subjects in the aliskiren 300 mg group (2 events) (hypertension, drug eruption).

Among the parameters relevant to “clinically notable changes in laboratory values” defined by the applicant, those that deviated from the laboratory’s normal ranges in at least 2 subjects of any group during the treatment period were as follows: white blood cell count increased (1.8% [2 of 112 subjects] in the placebo group, 1.8% [2 of 114 subjects] in the aliskiren 75 mg group, 0.9% [1 of 111 subjects] in the aliskiren 150 mg group, 0.9% [1 of 112 subjects] in the aliskiren 300 mg group), ALT increased (1.8% [2

of 112 subjects], 1.8% [2 of 114 subjects], 0% [0 of 111 subjects], and 0.9% [1 of 112 subjects], respectively), and potassium (K) increased (0% [0 of 112 subjects], 1.8% [2 of 114 subjects], 0% [0 of 111 subjects], and 0% [0 of 112 subjects], respectively). The incidences of these events were similar across all groups including the placebo group. The number of subjects with a serum K value < 3.5 mEq/L at any timepoint during the treatment period was highest in the placebo group (5.2% [6 of 115 subjects], 0% [0 of 115 subjects], 1.8% [2 of 112 subjects], and 0.9% [1 of 113 subjects], respectively) and there was no trend towards an increase in the incidence with increasing dose of aliskiren. Two subjects had a serum K value > 5.5 mEq/L at any timepoint during the treatment period (0.9% [1 of 115 subjects], 0% [0 of 115 subjects], 0% [0 of 112 subjects], and 0.9% [1 of 113 subjects], respectively), which were reported as adverse events (blood K increased), but a causal relationship to the study drug was denied. In these two subjects, no treatment was done for the adverse event and serum K returned to normal during the treatment period. None of the subjects had a "clinically notable value" of serum creatinine or BUN as defined by the applicant.

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

4.(iii).A.(3).1) Japanese phase III study (Attached document 5.3.5.1-2, Study 1301 [June 2006 to [redacted]])

A randomized, double-blind, placebo- and active-controlled, parallel-group study comparing aliskiren 150 mg to placebo and to losartan 50 mg was conducted at 53 centers in Japan to evaluate the efficacy, safety, and pharmacokinetics of aliskiren in Japanese patients with mild to moderate essential hypertension (Target sample size, 297 subjects in the aliskiren group, 297 subjects in the losartan group, 149 subjects in the placebo group, 743 cases in total). The primary objective of the study was to simultaneously test for the superiority of aliskiren over placebo and for the non-inferiority of aliskiren to losartan in terms of the primary endpoint of the change from baseline in trough msDBP at Week 8 (at the end of the treatment period) and a non-inferiority margin of 2.25 mmHg was chosen as 1/2 of the estimated difference between losartan and placebo in trough msDBP change, i.e., 4.5 mmHg.

All subjects received placebo during the run-in period (4 weeks) and aliskiren 150 mg, losartan 50 mg, or placebo was orally administered once daily at around 8:00 am (6:00-10:00 am) during the treatment period (8 weeks). The study drug was administered without regard to meals.

The main inclusion criteria were as follows: outpatients with essential hypertension who were aged ≥ 20 and < 75 at initial registration; and msDBP at Visit 2 (Day -14) and Visit 3 (Day 1) were "≥ 90 mmHg and < 110 mmHg" and "≥ 95 mmHg and < 110 mmHg," respectively, and the difference in msDBP between Visit 2 and Visit 3 was ≤ 10 mmHg. The exclusion criteria were as follows: secondary hypertension, severe hypertension, any condition affecting drug absorption, and serious diseases/symptoms.

All of 761 randomized subjects (156 subjects in the placebo group, 302 subjects in the aliskiren group, 303 subjects in the losartan group) were included in the safety analysis and the FAS and the FAS was the primary efficacy analysis population. Of the 761 randomized subjects, 50 subjects (15 subjects, 14 subjects,

and 21 subjects, respectively) prematurely discontinued study medication during the treatment period due to the occurrence of adverse events (20 subjects), abnormalities in physical examination etc. that were not classified as adverse events (20 subjects), consent withdrawal (7 subjects), etc. and 711 subjects completed the study.

The primary efficacy endpoint of change from baseline in trough msDBP at Week 8 (LOCF) in the FAS is presented in Table 2 and the results of between-group comparison of changes (Week 8 − Baseline) in Table 3. As to comparison between aliskiren and placebo groups, the least squares mean difference between aliskiren and placebo in trough msDBP change from baseline at Week 8 (aliskiren group − placebo group) (95% CI), based on an ANCOVA model including baseline msDBP as a covariate and treatment and region as factors, was -5.91 mmHg (-7.55 to -4.27) and the absolute change in msDBP was significantly greater in the aliskiren group than in the placebo group ($P < 0.0001$, ANCOVA), demonstrating the superiority of aliskiren 150 mg over placebo. As to comparison between aliskiren and losartan groups, the least squares mean difference between aliskiren and losartan in trough msDBP change from baseline at Week 8 (aliskiren group − losartan group) (95% CI), based on an ANCOVA model including baseline msDBP as a covariate and treatment and region as factors, was -0.16 mmHg (-1.51 to 1.20) and the upper limit of the 95% confidence interval did not exceed the non-inferiority margin (2.25 mmHg), demonstrating the non-inferiority of aliskiren 150 mg to losartan 50 mg.

Table 2. Change from baseline in trough msDBP at Week 8 (LOCF) (Adapted from CTD)

		Placebo	Aliskiren	Losartan
		N = 156	N = 302	N = 303
Baseline	**Mean ± SD**	**98.7 ± 3.83**	**98.9 ± 3.73**	**99.4 ± 4.22**
	Median	**97.2**	**97.8**	**98.0**
	Min-Max	**94.7-109.3**	**94.7-109.3**	**94.7-109.3**
Week 8	**Mean ± SD**	**95.7 ± 9.27**	**89.9 ± 10.37**	**90.8 ± 9.38**
	Median	**95.3**	**90.0**	**90.0**
	Min-Max	**67.3-121.7**	**53.0-116.7**	**66.0-124.3**
Change from baseline	**Mean ± SD**	**-3.0 ± 8.18**	**-8.9 ± 9.43**	**-8.7 ± 8.02**
	Least squares mean* (SE)	**-3.0 (0.69)**	**-8.9 (0.49)**	**-8.7 (0.50)**

Unit: mmHg

* Based on an ANCOVA model including baseline msDBP as a covariate and treatment and region as factors

Table 3. Between-group comparison of changes from baseline in trough msDBP at Week 8 (LOCF) (Adapted from CTD)

Comparison	Least squares mean difference * (SE)	95% CI*
Aliskiren 150 mg vs. Placebo	**-5.91 (0.84)**	**-7.55 to -4.27**
Aliskiren 150 mg vs. Losartan 50 mg	**-0.16 (0.69)**	**-1.51 to 1.20**
Losartan 50 mg vs. Placebo	**-5.76 (0.84)**	**-7.40 to -4.11**

Unit: mmHg

* Based on an ANCOVA model including baseline msDBP as a covariate and treatment and region as factors

The secondary endpoint of the change from baseline in msSBP at Week 8 (LOCF) (Week 8 − Baseline) in the FAS was -1.4 ± 11.56 mmHg (mean ± SD) in the placebo group, -10.2 ± 13.10 mmHg in the aliskiren group, and -10.4 ± 12.72 mmHg in the losartan group. As to comparison between aliskiren and placebo,

the least squares mean difference between aliskiren and placebo in msSBP change from baseline at Week 8 (aliskiren group − placebo group) (95% CI), based on an ANCOVA model including baseline msSBP as a covariate and treatment and region as factors, was -8.38 mmHg (-10.76 to -6.01) and the absolute change in msSBP was significantly greater in the aliskiren group than in the placebo group ($P < 0.0001$, ANCOVA). As to comparison between aliskiren and losartan, the least squares mean difference between aliskiren and losartan in msSBP change from baseline at Week 8 (aliskiren group − losartan group) (95% CI), based on an ANCOVA model including baseline msSBP as a covariate and treatment and region as factors, was 0.14 mmHg (-1.82 to 2.10).

The incidence of adverse events during the treatment period was 42.3% (66 of 156 subjects) in the placebo group, 50.3% (152 of 302 subjects) in the aliskiren group, and 46.5% (141 of 303 subjects) in the losartan group. Adverse events reported by at least 2.0% of subjects in any group during the treatment period are shown in Table 4.

Table 4. Common adverse events during the treatment period (Adapted from CTD)

Adverse event	Placebo	Aliskiren	Losartan
	N = 156	N = 302	N = 303
	n (%)		
Nasopharyngitis	13 (8.3)	48 (15.9)	40 (13.2)
Blood TG increased	3 (1.9)	9 (3.0)	8 (2.6)
Headache	6 (3.8)	9 (3.0)	10 (3.3)
Occult blood positive	5 (3.2)	9 (3.0)	6 (2.0)
γ-GTP increased	2 (1.3)	8 (2.6)	2 (0.7)
Blood CK increased	2 (1.3)	7 (2.3)	17 (5.6)
ALT increased	2 (1.3)	6 (2.0)	11 (3.6)
Hyperuricaemia	1 (0.6)	6 (2.0)	2 (0.7)
AST increased	2 (1.3)	1 (0.3)	7 (2.3)

No deaths occurred. Serious adverse events during the treatment period were myocardial infarction (placebo group) and brain stem infarction (losartan group) and their causal relationship to the study drug was denied. There were no serious adverse events in the aliskiren group.

Adverse events leading to discontinuation during the treatment period occurred in 19 subjects: 7 subjects in the placebo group (7 events) (myocardial infarction, blood pressure increased [3 events], gastroenteritis, systolic blood pressure increased, headache), 5 subjects in the aliskiren group (6 events) (head discomfort, headache, blood pressure increased, arthralgia, dizziness, vomiting), and 7 subjects in the losartan group (8 events) (brain stem infarction, blood pressure increased [2 events], paroxysmal tachycardia, hepatic function abnormal, gastritis, muscle cramp, blood CK increased).

Among the parameters relevant to “clinically notable changes in laboratory values” defined by the applicant, those that deviated from the laboratory’s normal ranges during the treatment period were as follows: white blood cell count increased (> 50%) (0% [0 of 155 subjects] in the placebo group, 0.3% [1 of 302 subjects] in the aliskiren group, 0% (0 of 302 subjects) in the losartan group), K increased (> 20%) (1.9% [3 of 155 subjects], 0.7% [2 of 302 subjects], and 0.7% [2 of 302 subjects], respectively), K

decreased (> 20%) (0% [0 of 155 subjects], 0% [0 of 302 subjects], and 0.3% [1 of 302 subjects], respectively), Ca increased (> 10%) (0% [0 of 155 subjects], 0.3% [1 of 302 subjects], and 0% [0 of 302 subjects], respectively), AST increased (> 150%) (0% [0 of 155 subjects], 0.3% [1 of 302 subjects], and 1.3% [4 of 302 subjects], respectively), ALT increased (> 150%) (0% [0 of 155 subjects], 0.3% [1 of 302 subjects], and 1.0% [3 of 302 subjects], respectively), bilirubins total increased (> 100%) (0% [0 of 155 subjects], 0.7% [2 of 302 subjects], and 1.0% [3 of 302 subjects], respectively), uric acid increased (> 50%) (0% [0 of 155 subjects], 0% [0 of 302 subjects], and 0.3% [1 of 302 subjects], respectively), and CK increased (> 300%) (0.6% [1 of 155 subjects], 0.3% [1 of 302 subjects], and 2.0% [6 of 302 subjects], respectively). White blood cell count increased (> 50%) and Ca increased (> 10%) were observed in the aliskiren group only. Except that the incidences of AST increased (> 150%), ALT increased (> 150%), and CK increased (> 300%) were higher in the losartan group than in the other two groups, there were no major differences among the groups. The incidence of increases in serum K > 5.5 mEq/L at any timepoint during the treatment period was 0.6% (1 of 155 subjects) in the placebo group, 0.7% (2 of 302 subjects) in the aliskiren group, and 0% in the losartan group. A serum K value of ≥ 6.0 mEq/L was noted in the aliskiren group and its incidence was 0.3% (1 of 302 subjects). None of the subjects in any group had a "clinically notable value" of BUN or serum creatinine.

4.(iii).A.(3).2) Foreign phase III study (Attached document 5.3.5.1-3, Study 2308 [November 2004 to [redacted] 20[redacted]])

A randomized, double-blind, parallel-group, comparative study was conducted at a total of 69 centers in Canada, Guatemala, Korea, Netherlands, and the US to test for the superiority of aliskiren 150, 300, and 600 mg over placebo in lowering blood pressure in patients with mild to moderate essential hypertension, using msDBP as the primary efficacy endpoint (Target sample size: 612).

The main inclusion criteria were as follows: outpatients with essential hypertension aged ≥18 years; and msDBP at Visit 2 (Day -28 or -14) and Visit 3 (Day 1) were "≥ 90 mmHg and < 110 mmHg" and "≥ 95 mmHg and < 110 mmHg," respectively, and the difference in msDBP between Visit 2 and Visit 3 was ≤ 10 mmHg. The exclusion criteria were as follows: secondary hypertension, severe hypertension,any condition affecting drug absorption, and serious diseases/symptoms.

The study consisted of a 2-week screening/washout period, a 2- to 4-week run-in period (placebo administration), an 8-week treatment period, and a 2-week withdrawal period and the study drug was orally administered once daily at around 8:00 am.

All of the 672 randomized subjects (165 subjects in the placebo group, 172 subjects in the aliskiren 150 mg group, 169 subjects in the aliskiren 300 mg group, 166 subjects in the aliskiren 600 mg group) were included in the safety analysis, of whom 662 subjects (163 subjects, 167 subjects, 166 subjects, and 166 subjects, respectively) were included in the intention-to-treat (ITT) population for the primary efficacy analysis.

The primary efficacy endpoint of change from baseline in trough msDBP at Week 8 (LOCF) in the ITT population is presented in Table 5 and the results of between-group comparison of changes (Week 8 − Baseline) in Table 6.

Table 5. Change from baseline in trough msDBP at Week 8 (LOCF) (Adapted from CTD)

		Placebo	Aliskiren 150 mg	Aliskiren 300 mg	Aliskiren 600 mg
		N = 163	N = 167	N = 166	N = 166
Baseline	**Mean ± SD**	**99.4 ± 3.6**	**99.7 ± 3.6**	**99.7 ± 3.9**	**99.4 ± 3.5**
Week 8	**Mean ± SD**	**94.6 ± 9.7**	**89.5 ± 8.3**	**88.6 ± 8.4**	**87.0 ± 9.0**
Change from baseline (Week 8 − Baseline)	**Mean ± SD**	**-4.8 ± 8.6**	**-10.2 ± 7.4**	**-11.0 ± 8.0**	**-12.4 ± 7.8**
	Least squares mean* (SE)	**-4.92 (0.64)**	**-10.33 (0.63)**	**-11.10 (0.64)**	**-12.52 (0.64)**

Unit: mmHg

* Based on an ANCOVA model including baseline msDBP as a covariate and treatment and region as factors

Table 6. Between-group comparison of changes from baseline in trough msDBP at Week 8 (LOCF) (Adapted from CTD)

Comparison	Least squares mean difference* (SE)	95% CI*	*P*-value*
Aliskiren 150 mg vs. Placebo	**-5.40 (0.87)**	**-7.11 to -3.70**	***P* < 0.0001**
Aliskiren 300 mg vs. Placebo	**-6.18 (0.87)**	**-7.88 to -4.47**	***P* < 0.0001**
Aliskiren 600 mg vs. Placebo	**-7.60 (0.87)**	**-9.30 to -5.89**	***P* < 0.0001**

Unit: mmHg

*ANCOVA including baseline msDBP as a covariate and treatment and region as factors (pairwise comparisons unadjusted for multiplicity)

Ambulatory blood pressure monitoring (ABPM) was performed in 216 subjects (53 subjects in the placebo group, 52 subjects in the aliskiren 150 mg group, 56 subjects in the aliskiren 300 mg group, 55 subjects in the aliskiren 600 mg group) and the change from baseline in 24-hour mean ambulatory diastolic blood pressure (MADBP) (the average of the 24 hourly MADBPs) at Week 8 (Week 8 − Baseline) was 1.61 ± 0.67 (least squares mean ± SE, based on a repeated-measures ANCOVA model including baseline 24-hour MADBP as a covariate, treatment, region, and post-dosing hour as factors, and treatment by post-dosing-hour interaction) in the placebo group, -6.55 ± 0.67 in the aliskiren 150 mg group, -5.96 ± 0.66 in the aliskiren 300 mg group, and -7.43 ± 0.66 mmHg in the aliskiren 600 mg group. The 24-hour MADBP trough-to-peak ratios (T/P ratio) in the aliskiren 150, 300, and 600 mg groups were 0.64, 0.98, and 0.86, respectively.

The incidence of adverse events during the treatment period was 43.0% (71 of 165 subjects) in the placebo group, 40.1% (69 of 172 subjects) in the aliskiren 150 mg group, 46.7% (79 of 169 subjects) in the aliskiren 300 mg group, and 52.4% (87 of 166 subjects) in the aliskiren 600 mg group. Adverse events reported by at least 2.0% of subjects in any group during the treatment period are shown in Table 7.

Table 7. Common adverse events during the treatment period (Adapted from CTD)

Adverse event	Placebo	Aliskiren 150 mg	Aliskiren 300 mg	Aliskiren 600 mg
	N = 165	N = 172	N = 169	N = 166
	n (%)			
Headache	16 (9.7)	12 (7.0)	13 (7.7)	9 (5.4)
Nasopharyngitis	10 (6.1)	5 (2.9)	6 (3.6)	3 (1.8)
Upper respiratory tract infection	7 (4.2)	4 (2.3)	4 (2.4)	5 (3.0)
Back pain	4 (2.4)	2 (1.2)	0 (0.0)	1 (0.6)
Diarrhoea	2 (1.2)	2 (1.2)	3 (1.8)	19 (11.4)
Dizziness	7 (4.2)	2 (1.2)	9 (5.3)	5 (3.0)
Nausea	4 (2.4)	2 (1.2)	3 (1.8)	0 (0.0)
Epistaxis	1 (0.6)	1 (0.6)	0 (0.0)	4 (2.4)
Constipation	1 (0.6)	0 (0.0)	0 (0.0)	6 (3.6)
Fatigue	1 (0.6)	0 (0.0)	2 (1.2)	5 (3.0)

The incidence of adverse events during the withdrawal period was 13.3% (18 of 135 subjects) in the placebo group, 17.9% (29 of 162 subjects) in the aliskiren 150 mg group, 11.3% (18 of 159 subjects) in the aliskiren 300 mg group, and 14.5% (22 of 152 subjects) in the aliskiren 600 mg group and there were no major differences among the groups. None of the subjects in the aliskiren groups experienced adverse events of “blood pressure increased” during the withdrawal period.

No deaths occurred. A total of 8 subjects experienced serious adverse events (2 subjects during the screening/washout period, 1 subject during the run-in period, 4 subjects during the treatment period, 1 subject during the withdrawal period). Serious adverse events reported during the treatment period include angina unstable and blood pressure increased (1 subject in the aliskiren 150 mg group), appendicitis (1 subject in the aliskiren 300 mg group), depression (1 subject in the aliskiren 300 mg group), and pain (1 subject in the aliskiren 600 mg group). A causal relationship to the study drug was denied for all events except for depression. The outcome of depression was reported as “improved.” During the periods other than the treatment period, serious adverse events of subarachnoid haemorrhage due to cerebral artery rupture (screening/washout period), small intestinal obstruction (screening/washout period), bladder cancer (run-in period), and venous occlusion (withdrawal period) occurred, but a causal relationship to the study drug was denied for all events.

Adverse events leading to discontinuation during the treatment period occurred in 12 subjects: 6 subjects in the placebo group (14 events) (headache [4 events], lethargy, dizziness [2 events], muscle twitching, diarrhoea, hypotension, nausea, urticaria, blood pressure increased, duodenal ulcer), 1 subject in the aliskiren 150 mg group (1 event) (sense of oppression), 3 subjects in the aliskiren 300 mg group (3 events) (dizziness, mood alterations, rash), and 2 subjects in the aliskiren 600 mg group (3 events) (flatulence, constipation, diarrhoea).

Multiple hematology parameters were relevant to “clinically notable changes in laboratory values” defined by the applicant, but these changes were within the laboratory’s normal ranges in most cases. Multiple

clinical chemistry parameters were also relevant to “clinically notable changes in laboratory values” defined by the applicant, but there was no consistent trend towards an increase in the incidence with increasing dose of aliskiren, for any parameter. There were 3 subjects with a serum K value > 5.5 mmol/L (1 of 152 subjects in the placebo group [0.7%], 2 of 157 subjects in the aliskiren 150 mg group [1.3%]) and 13 subjects with a serum K value < 3.5 mmol/L (6 of 152 subjects in the placebo group [3.9%], 3 of 157 subjects in the aliskiren 150 mg group [1.9%], 2 of 166 subjects in the aliskiren 300 mg group [1.2%], 2 of 157 subjects in the aliskiren 600 mg group [1.3%]) at any timepoint during the treatment period, but none of these cases were reported as adverse events.

4.(iii).A.(3).3) Japanese long-term treatment study (Attached document 5.3.5.2-1, Study 1202 [November 2004 to [redacted] 20[redacted]])

An open-label, uncontrolled study consisting of a dose titration period (8 weeks) and a fixed dose/combination treatment period (44 weeks) was conducted at 30 centers in Japan to evaluate the safety, tolerability, and efficacy of aliskiren administered once daily for 52 weeks in Japanese patients with essential hypertension (Target sample size: 300).

The main inclusion criteria were patients with essential hypertension who were judged by the investigator or sub-investigator to have no safety problems and be able to continue treatment with aliskiren, based on the results of the preceding study 1201. A 1-week washout period was included between Study 1201 and this study. During the dose titration period in this study, all subjects received aliskiren 75 mg once daily at Week 0 and when trough msDBP exceeded 90 mmHg at Week 2, 4, or 6, the dose of aliskiren was up-titrated to 150 mg and then to 300 mg in a stepwise manner. In the case where the dose of aliskiren at Week 4 was 300 mg, however, even when trough msDBP at Week 6 exceeded 90 mmHg, the dose was maintained at 300 mg. After Week 8 in the fixed dose/combination treatment period, the dose of aliskiren at Week 6 was maintained. However, when trough msDBP exceeded 90 mmHg at 2 consecutive visits, concomitant use or dose increase of diuretics or Ca antagonists was permitted. The study drug was to be administered before breakfast at around 8:00 am.

Of subjects who completed Study 1201, 345 subjects were enrolled in the dose titration period of this study and 344 subjects excluding 1 subject who did not receive the study drug were included in the safety analysis and the FAS, which was the efficacy analysis population. The numbers of all subjects, subjects treated with aliskiren alone, subjects treated with aliskiren in combination with Ca antagonist, and subjects treated with aliskiren in combination with diuretic (the numbers of enrollment) and the status of the study are presented in Table 8. The main reasons for discontinuation during the treatment period were adverse events (7.0% [24 of 345 subjects]), protocol violations (2.9% [10 of 345 subjects]), and consent withdrawal (2.3% [8 of 345 subjects]).

Table 8. Disposition of subjects (Adapted from CTD)

	All subjects	Aliskiren alone	Aliskiren/Ca antagonist	Aliskiren/diuretic
	n (%)			
Enrollment	**345 (100.0)**	**175 (100.0)**	**90 (100.0)**	**79 (100.0)**
Study drug taken	**344 (99.7)**	**175 (100.0)**	**90 (100.0)**	**79 (100.0)**
Treatment period completed	**299 (86.7)**	**149 (85.1)**	**81 (90.0)**	**69 (87.3)**
Discontinuation during the treatment period	**46 (13.3)**	**26 (14.9)**	**9 (10.0)**	**10 (12.7)**

The primary efficacy endpoint of change from baseline in trough msDBP at Week 52 (LOCF) in the FAS (Week 52 − Baseline) when baseline was defined as Week 0 of Study 1201 or Week 0 of Study 1202 is shown in Table 9. The mean trough msDBP fell below 90 mmHg after Week 12 and trough msDBP at Week 28 (316 evaluable subjects) and at Week 52 (300 evaluable subjects) were 85.5 and 86.2 mmHg, respectively. At Week 52 (LOCF), 95 subjects were on 75 mg of aliskiren, 65 subjects were on 150 mg of aliskiren, and 184 subjects were on 300 mg of aliskiren. The change from the start of Study 1201 in msDBP by the final dose of aliskiren was -14.8 ± 9.0 (mean ± SD) at 75 mg, -11.4 ± 6.79 at 150 mg, and -12.3 ± 8.18 mmHg at 300 mg.

Table 9. Change from baseline (Study 1201, Study 1202) in msDBP at Week 52 (LOCF) (Adapted from CTD)

		FAS N = 344	
Definition of baseline		**Week 0 of Study 1201**	**Week 0 of Study 1202**
Baseline	**Mean ± SD**	**99.5 ± 3.98**	**94.1 ± 9.20**
Week 52	**Mean ± SD**	**86.6 ± 8.19**	**86.6 ± 8.19**
Change (Week 52 − Baseline)	**Mean ± SD**	**-12.8 ± 8.25**	**-7.5 ± 9.85**

Unit: mmHg

The incidence of adverse events during the treatment period was 85.2% (293 of 344 subjects). When adverse events were classified by preferred term (PT), the incidence of nasopharyngitis (45.6% [157 of 344 subjects]) was highest, followed by blood TG increased (6.4% [22 of 344 subjects]), back pain (4.9% [17 of 344 subjects]), and γ-GTP increased (4.9% [17 of 344 subjects]). The incidence of adverse events by dose level of aliskiren was 36.6% (126 of 344 subjects) at 75 mg, 39.0% (97 of 249 subjects) at 150 mg, and 82.6% (152 of 184 subjects) at 300 mg.

The incidence of adverse events by treatment was 72.7% (250 of 344 subjects) with aliskiren alone, 72.3% (86 of 119 subjects) with aliskiren/Ca antagonist combination, and 69.2% (63 of 91 subjects) with aliskiren/diuretic combination and there were no major differences among the treatments. When adverse events were classified by PT, the incidences of blood uric acid increased and hyperuricaemia were higher with aliskiren/diuretic combination than with the other treatments.

No deaths occurred. Serious adverse events were reported by a total of 13 subjects (9 subjects during the treatment period, 5 subjects during the follow-up period for serious adverse events [1 subject had a serious adverse event during both periods]). The 9 subjects with serious adverse events during the treatment period

include 5 subjects on aliskiren alone (2 subjects on aliskiren 75 mg, 2 subjects on aliskiren 150 mg, 1 subject on aliskiren 300 mg), 1 subject on aliskiren/Ca antagonist combination, 2 subjects on aliskiren/diuretic combination, and 1 subject on aliskiren/Ca antagonist/diuretic combination. Of the 9 subjects, 7 discontinued study medication due to serious adverse events. The serious adverse events reported during the treatment period include blood pressure increased, brain stem infarction, herpes zoster, calculus ureteric, malignant neoplasm/rectal cancer, acute myocardial infarction, joint dislocation, intervertebral disc protrusion, and rectal cancer. However, the time to onset of malignant neoplasm in the subject with malignant neoplasm/rectal cancer is unknown. A causal relationship to the study drug could not be denied for brain stem infarction, malignant neoplasm, and acute myocardial infarction. Except for the 1 subject with malignant neoplasm/rectal cancer, all subjects had recovered or improved at a follow-up. The 5 serious adverse events reported after the end of the study include brain stem infarction, haemorrhoids, epistaxis, ovarian cyst, and extradural abscess. Extradural abscess occurred in the same subject who had intervertebral disc protrusion during the treatment period. A causal relationship of brain stem infarction to the study drug could not be denied.

Baseline was defined as Week 0 of Study 1202 and clinical laboratory values during the treatment period after baseline were assessed. As a result, a hematology parameter relevant to “clinically notable changes in laboratory values” (defined by the applicant) occurring at an incidence of ≥ 2.0% was white blood cell count increased (7.3%) (25 of 344 subjects). Clinical chemistry parameters relevant to “clinically notable changes in laboratory values” (defined by the applicant) occurring at an incidence of ≥ 2.0% were as follows, in the descending order of incidence: bilirubin increased (15.1%) (52 of 344 subjects), BUN increased (11.0%) (38 of 344 subjects), ALT increased (5.5%) (19 of 344 subjects), K increased (4.4%) (15 of 344 subjects), K decreased (3.8%) (13 of 344 subjects), CK increased (2.3%) (8 of 344 subjects), and Ca decreased (2.0%) (7 of 344 subjects). At any timepoint during the treatment period, 2.0% of the subjects (7 of 344 subjects) had a serum K value < 3.5 mEq/L, 0.3% of the subjects (1 of 344 subjects) had a serum K value > 5.5 mEq/L, 0.3% of the subjects (1 of 344 subjects) had BUN > 40 mg/dL, and 0.3% of the subjects (1 of 344 subjects) had serum creatinine > 2 mg/dL, but there were no laboratory adverse events leading to study drug discontinuation or other serious adverse events.

ECG findings changed from “normal” at baseline (at the start of Study 1202) to “clinically significant abnormalities” during the treatment period in 1.2% of the subjects (4 of 344 subjects) and from “clinically insignificant abnormalities” at baseline (at the start of Study 1202) to “clinically significant abnormalities” in 0.3% of the subjects (1 of 344 subjects), which were not classified as adverse events.

4.(iii).A.(3).4) Study in Japanese hypertensive patients with renal impairment (Attached document 5.3.5.2-2, Study 1303 [20 to 20])

An open-label, uncontrolled study was conducted at 23 centers in Japan to evaluate the safety, efficacy, and pharmacokinetics of aliskiren administered once daily for 8 weeks in Japanese hypertensive patients with renal impairment (Target sample size: 38).

All subjects received placebo during the run-in period. The starting dose of aliskiren during the treatment period was 75 mg and if trough msSBP did not fall below 140 mmHg and/or trough msDBP did not fall below 90 mmHg at the specified timepoints during the treatment period and there were no safety concerns (serum K value > 5.5 mEq/L, ≥ 20% increase in serum creatinine, etc.), the dose was increased to 150 mg and then to 300 mg in a stepwise manner. The study drug was administered once daily at around 8:00 am.

The main inclusion criteria were as follows: outpatients aged ≥ 20 and ≤ 80 at initial registration; and serum creatinine at Visit 1 was ≥ 1.3 mg/dL and < 3.0 mg/dL for men or ≥ 1.2 mg/dL and < 3.0 mg/dL for women. The inclusion criterion for blood pressure was the same as in Study 1201.

Of 78 subjects enrolled in the run-in period, 38 subjects were discontinued during the run-in period (abnormalities in physical examination etc. that were not classified as adverse events [26 subjects], abnormalities in routine laboratory tests that were not classified as adverse events [6 subjects], etc.) and 40 subjects entered the treatment period. All of the 40 subjects were included in the safety analysis and the FAS, which was the efficacy analysis population. Of the 40 subjects, 5 subjects discontinued study medication during the treatment period due to the occurrence of adverse events (3 subjects) and consent withdrawal (2 subjects) and 35 subjects completed the study.

The efficacy endpoint of changes from baseline in trough msDBP and msSBP at Week 8 (LOCF) in the FAS is shown in Table 10. At Week 8, 9 subjects were on aliskiren 75 mg, 4 subjects were on aliskiren 150 mg, and 27 subjects were on aliskiren 300 mg.

Table 10. Changes from baseline in trough msDBP and msSBP at Week 8 (LOCF) (Adapted from CTD)

		FAS N = 40	
		msDBP	msSBP
Baseline	**Mean ± SD**	**99.3 ± 3.69**	**163.3 ± 11.71**
Week 8	**Mean ± SD**	**87.7 ± 9.88**	**149.4 ± 17.90**
Change from baseline (Week 8 − Baseline)	**Mean ± SD**	**-11.6 ± 9.73**	**-13.9 ± 16.57**

Unit: mmHg

The incidence of adverse events during the treatment period was 52.5% (21 of 40 subjects) and adverse events reported by at least 2 subjects were nasopharyngitis, back pain, and dizziness (2 subjects each). When the occurrence of adverse events by subject was examined, there was no particular trend towards increased adverse events or increased moderate or severe adverse events due to an increased dose of aliskiren.

No deaths occurred. Serious adverse events reported include cerebral infarction and urinary retention (one subject each). A causal relationship of cerebral infarction to the study drug could not be denied and this event improved after study drug discontinuation. A causal relationship of urinary retention to the study drug was denied and this event resolved during the study. During the follow-up period for serious adverse

events, cystitis occurred in the subject who had urinary retention during the treatment period and its causal relationship to the study drug was denied and then recovery was confirmed.

Adverse events leading to discontinuation during the treatment period were blood pressure increased (1 subject), cerebral infarction (1 subject), and protein urine (1 subject).

For all urinalysis parameters, the percentage of subjects with abnormalities was similar between at baseline and at Week 8 and no worsening was observed. “Clinically notable changes in laboratory values” (defined by the applicant) were K increased (15.0%) (6 of 40 subjects), BUN increased (10.0%) (4 of 40 subjects), AST increased (2.6%) (1 of 39 subjects), ALT increased (2.6%) (1 of 39 subjects), Na decreased (2.5%) (1 of 40 subjects), and Cl increased (2.5%) (1 of 40 subjects). At any time point during the treatment period, 15.0% of the subjects (6 of 40 subjects) had a serum K value > 5.5 mEq/L and 7.5% of the subjects (3 of 40 subjects) had a serum K value ≥ 6.0 mEq/L, but none of these cases were classified as adverse events. There were no laboratory adverse events (SOC of investigations) leading to discontinuation or serious adverse events.

Renal function laboratory testing focused on serum creatinine, BUN, CCr, and urine protein/creatinine ratio. With respect to change over time by subject, none of the subjects had > 50% or > 20% increase from baseline in serum creatinine. BUN was increased by > 50% from baseline in 4 subjects. Urine protein/creatinine ratio approximately doubled from baseline in 2 subjects. CCr was not worsened markedly from baseline throughout the study period in any subject. None of these laboratory changes were classified as adverse events [see “4.(ii).A.(3).3) Pharmacokinetic evaluation in Japanese hypertensive patients with renal impairment” for pharmacokinetic data].

4.(iii).A.(3).5) Study in patients with severe hypertension (Attached document 5.3.5.2-3, Study 1304 [April to [redacted] 2006])

An open-label, uncontrolled study was conducted at 9 centers in Japan to evaluate the safety and efficacy of aliskiren administered once daily for 8 weeks in Japanese patients with severe hypertension (Target sample size: 38).

The main inclusion criteria were as follows: outpatients with severe hypertension (msDBP ≥ 110 mmHg or msSBP ≥ 180 mmHg at 2 timepoints during the run-in period) aged ≥ 20 and ≤ 80 years at initial enrollment; and the differences in msSBP and in msDBP between 2 timepoints during the run-in period were ≤ 20 and ≤ 10 mmHg, respectively.

Of 46 subjects enrolled in the run-in period, 7 subjects were discontinued during the run-in period (abnormalities in physical examination etc. that were not classified as adverse events [5 subjects] etc.) and 39 subjects entered the treatment period. All of the 39 subjects were included in the safety analysis and the FAS, which was the efficacy analysis population. No subject discontinued study medication during the treatment period and all of the 39 subjects completed the study.

Following a 2-week run-in period (placebo administration), treatment was started with aliskiren 150 mg during a 8-week treatment period and after Visit 4 (Week 2), when trough msSBP was ≥ 160 mmHg or trough msDBP was ≥ 100 mmHg and aliskiren was tolerated, the dose was increased to 300 mg. After Visit 5 (Week 4), when trough msSBP was ≥ 140 mmHg or trough msDBP was ≥ 90 mmHg, the investigator etc. considered the safety and antihypertensive effect of aliskiren and then the dose was increased to 300 mg, as appropriate. However, dose reduction of the study drug was not permitted.

Changes from baseline in trough msDBP and msSBP at Week 8 (LOCF) in the FAS are shown in Table 11. At Week 8, 6 subjects were on aliskiren 150 mg and 33 subjects were on aliskiren 300 mg.

Table 11. Changes from baseline in trough msDBP and msSBP at Week 8 (LOCF) (Adapted from CTD)

		FAS N = 39	
		msDBP	msSBP
Baseline	**Mean ± SD**	**111.6 ± 4.52**	**171.7 ± 11.72**
Week 8	**Mean ± SD**	**98.7 ± 11.00**	**151.1 ± 17.73**
Change from baseline (Week 8 − Baseline)	**Mean ± SD**	**-12.9 ± 10.43**	**-20.6 ± 11.97**

Unit: mmHg

The incidence of adverse events during the treatment period was 66.7% (26 of 39 subjects). Adverse events reported by at least 2 subjects during the treatment period were nasopharyngitis (12.8%) (5 of 39 subjects), blood uric acid increased (7.7%) (3 of 39 subjects), headache (7.7%) (3 of 39 subjects), protein urine present (7.7%) (3 of 39 subjects), blood creatinine increased (5.1%) (2 of 39 subjects), eczema (5.1%) (2 of 39 subjects), and hyperuricaemia (5.1%) (2 of 39 subjects). There were no deaths or serious adverse events.

There were no adverse events leading to treatment discontinuation.

"Clinically notable changes in laboratory values" (defined by the applicant) were Ca increased (5.1%) (2 of 39 subjects), white blood cell count increased (2.6%) (1 of 39 subjects), K increased (2.6%) (1 of 39 subjects), and bilirubins total increased (2.6%) (1 of 39 subjects). At any timepoint during the treatment period, 5.1% of the subjects (2 of 39 subjects) had a serum K value < 3.5 mEq/L, but their serum K values all returned to ≥ 3.5 mEq/L at the next measuring time during the treatment period. None of the subjects had BUN > 40 mg/dL or serum creatinine > 2.0 mg/dL.

4.(iii).A.(3).6) Study in elderly patients with essential hypertension (Attached document 5.3.5.1-4, Study 2324 [April 2005 to [redacted] 20[redacted]])

A randomized, double-blind, parallel-group, comparative study was conducted at a total of 62 centers in Argentina, Austria, France, Italy, Japan, Spain, and Sweden to test for the superiority of aliskiren 300 mg over aliskiren 75 mg in reducing blood pressure in patients ≥ 65 years of age with essential hypertension, using change from baseline in 24-hour mean ambulatory systolic blood pressure (MASBP) at Week 8 as

the primary endpoint (Target sample size: 356 subjects in total). In this study, patients were stratified by age (< 75 years, ≥ 75 years) at randomization.

The main inclusion criteria were as follows: outpatients with essential hypertension aged 65 or older; msSBP at Visit 2 during the run-in period was ≥ 140 mmHg and < 180 mmHg; msSBP at Visit 3 was ≥ 145 mmHg and < 180 mmHg; 24-hour MASBP at baseline was ≥ 135 mmHg; and the difference in msSBP between the last 2 timepoints during the run-in period was ≤ 15 mmHg.

All subjects received placebo during the run-in period (2 weeks or 4 weeks) and aliskiren 75, 150, and 300 mg or lisinopril 10 mg was administered once daily at around 8:00 am during the treatment period (8 weeks).

All of 355 randomized subjects (91 subjects in the aliskiren 75 mg group, 84 subjects in the aliskiren 150 mg group, 94 subjects in the aliskiren 300 mg group, 86 subjects in the lisinopril group) were included in the safety analysis, of whom 354 subjects (91 subjects, 84 subjects, 94 subjects, and 85 subjects, respectively) were included in the ITT population for primary efficacy analysis, except for 1 subject in the lisinopril group. In this study, the safety analysis population included 44 Japanese subjects (12 subjects, 11 subjects, 13 subjects, and 8 subjects, respectively) and the ITT population included 44 Japanese subjects (12 subjects, 11 subjects, 13 subjects, and 8 subjects, respectively).

The primary efficacy endpoint of change from baseline in 24-hour MASBP at Week 8 (LOCF) in the ITT population is shown in Table 12. The least squares mean difference between aliskiren 75 mg and aliskiren 300 mg (aliskiren 75 mg group − aliskiren 300 mg group) in 24-hour MASBP change (Week 8 − Baseline) (95% CI), based on a repeated measures ANCOVA model including baseline 24-hour MASBP as a covariate, treatment, region, age group, and post-dosing hour as factors, and treatment by post-dosing-hour interaction, was 0.32 mmHg (-1.88 to 2.52) and there were no significant differences in the absolute change in MASBP between the groups (P = 0.7763, ANCOVA).

Table 12. Change from baseline in 24-hour MASBP at Week 8 (LOCF) (Adapted from CTD)

		Aliskiren 75 mg N = 91	Aliskiren 150 mg N = 84	Aliskiren 300 mg N = 94	Lisinopril 10 mg N = 85
Baseline	**Mean ± SD**	**147.59 ± 13.431**	**148.04 ± 9.634**	**146.68 ± 9.082**	**149.16 ± 10.339**
Week 8	**Mean ± SD**	**138.63 ± 14.194**	**140.25 ± 11.682**	**137.88 ± 13.536**	**137.58 ± 12.313**
Change (Week 8 − Baseline)	**Mean ± SD**	**-8.95 ± 11.824**	**-7.79 ± 12.631**	**-8.80 ± 13.064**	**-11.58 ± 11.410**
	Least squares mean* (SE)	**-8.35 (0.83)**	**-7.06 (0.84)**	**-8.67 (0.80)**	**-10.19 (0.86)**

Unit: mmHg

* Based on a repeated measures ANCOVA model including baseline 24-hour MASBP as a covariate, treatment, region, age group, and post-dosing hour as factors, and treatment by post-dosing-hour interaction

For the secondary efficacy endpoint of change from baseline in 24-hour MADBP at Week 8 (LOCF) (Week 8 − Baseline) in the ITT population, the least squares mean difference between aliskiren 75 mg and

aliskiren 300 mg (aliskiren 75 mg group − aliskiren 300 mg group) (95% CI), based on a repeated measures ANCOVA model including baseline 24-hour MADBP as a covariate, treatment, region, age group, and post-dosing hour as factors, and treatment by post-dosing-hour interaction, was -0.59 (-1.95 to 0.77) and there were no significant differences in the absolute change in 24-hour MADBP between the groups (P = 0.3967, ANCOVA). The 24-hour MASBP T/P ratios in the aliskiren 75, 150, and 300 mg groups and lisinopril group were 0.77, 0.64, 0.79, and 0.87, respectively. msDBP and msSBP tended to decrease with increasing dose of aliskiren.

The incidence of adverse events during the treatment period was 29.7% (27 of 91 subjects) in the aliskiren 75 mg group, 40.5% (34 of 84 subjects) in the aliskiren 150 mg group, 24.5% (23 of 94 subjects) in the aliskiren 300 mg group, and 30.2% (26 of 86 subjects) in the lisinopril group and there was no trend towards an increased incidence with increasing dose of aliskiren. Adverse events with an incidence ≥ 2.0% in any of the treatment groups during the treatment period are shown in Table 13.

Table 13. Common adverse events during the treatment period (Adapted from CTD)

	Aliskiren 75 mg	Aliskiren 150 mg	Aliskiren 300 mg	Lisinopril 10 mg
	N = 91	N = 84	N = 94	N = 86
	n (%)			
Diarrhoea	0 (0.0)	3 (3.6)	4 (4.3)	1 (1.2)
Dyspepsia	2 (2.2)	1 (1.2)	2 (2.1)	1 (1.2)
Urinary tract infection	2 (2.2)	1 (1.2)	2 (2.1)	1 (1.2)
Cough	1 (1.1)	0 (0.0)	1 (1.1)	2 (2.3)
Nasopharyngitis	2 (2.2)	2 (2.4)	1 (1.1)	2 (2.3)
Vertigo	1 (1.1)	2 (2.4)	1 (1.1)	1 (1.2)
Abdominal pain	1 (1.1)	2 (2.4)	0 (0.0)	0 (0.0)
Asthenia	2 (2.2)	4 (4.8)	0 (0.0)	2 (2.3)
Dizziness	3 (3.3)	5 (6.0)	0 (0.0)	2 (2.3)
Headache	3 (3.3)	2 (2.4)	0 (0.0)	5 (5.8)
Influenza	0 (0.0)	4 (4.8)	0 (0.0)	1 (1.2)
Migraine	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.3)
Palpitations	2 (2.2)	1 (1.2)	0 (0.0)	0 (0.0)

Two deaths occurred. One subject died due to abdominal aneurysm during the washout period and 1 subject on aliskiren 75 mg during the treatment period died due to colon cancer during the follow-up period for serious adverse events. A causal relationship to the study drug was denied for both deaths. Serious adverse events reported during the treatment period were transient ischaemic attack (1 subject in the aliskiren 150 mg group) and prostate cancer (1 subject in the aliskiren 300 mg group) and a causal relationship to the study drug was denied for both cases. While transient ischaemic attack had resolved by the end of the study, prostate cancer was still ongoing at the end of the study. A serious adverse event reported during the follow-up period for serious adverse events was erythema multiforme which developed 4 days after the completion of study treatment (1 subject in the aliskiren 75 mg group) and its causal relationship to either the study drug or therapeutic drugs after the completion of study treatment could not be denied. This event had resolved 23 days after the completion of study treatment.

Adverse events leading to discontinuation during the treatment period occurred in 13 subjects: 5 subjects in the aliskiren 75 mg group (5 events) (pruritus, hypertensive crisis, hypertension, blood pressure increased, vertigo), 2 subjects in the aliskiren 150 mg group (2 events) (hypertensive crisis, transient ischaemic attack), 1 subject in the aliskiren 300 mg group (1 event) (hypertension), and 5 subjects in the lisinopril 10 mg group (9 events) (cough, dyspnoea, constipation, dyspepsia, hypertension, vertigo, eczema, feeling hot, erythema).

Although there were subjects with K increased or BUN increased that met the definition of "clinically notable changes in laboratory values," these changes were within the laboratory's normal ranges in most cases. At any timepoint during the treatment period, 1 subject (lisinopril group) had a serum K value < 3.5 mmol/L and 5 subjects (3 subjects in the aliskiren 75 mg group, 1 subject in the aliskiren 150 mg group, 1 subject in the aliskiren 300 mg group) had a serum K value > 5.5 mmol/L, but none of these cases were classified as adverse events.

4.(iii).A.(4) Other studies

4.(iii).A.(4).1) Study assessing the occurrence of epithelial hyperplasia in the colon in healthy volunteers (Attached document 5.3.3.1-5, Study 2103 [to 20], Reference data)

A randomized, double-blind, parallel-group, comparative study was conducted at 3 centers in the US to determine the occurrence of epithelial hyperplasia in mucosal biopsy sections obtained from the colon in healthy volunteers orally treated with aliskiren 300 mg once daily for 8 weeks compared to those treated with placebo (Target sample size: 10 subjects in the placebo group, 20 subjects in the aliskiren group, 30 subjects in total).

Thirty-one healthy volunteers (patients with uncomplicated mild to moderate hypertension were allowed to be enrolled into the study) who were considered eligible for the study (men or women aged ≥ 21 and ≤ 65; and colonoscopy and microscopy of biopsy samples at screening showed no adenomatous polyp or inflammation) were enrolled into the study (10 subjects in the placebo group, 21 subjects in the aliskiren group) and all of them were included in the safety analysis. Thirty subjects (10 subjects in the placebo group, 20 subjects in the aliskiren group) completed the study and were included in colonoscopic assessment. One subject in the aliskiren group prematurely discontinued study medication due to a protocol violation.

The incidence of adverse events was 30.0% (3 of 10 subjects) in the placebo group and 47.6% (10 of 21 subjects) in the aliskiren group and adverse events reported by at least 2 subjects in either group were diarrhoea (0 of 10 subjects and 3 of 21 subjects, respectively), vomiting (0 of 10 subjects and 2 of 21 subjects, respectively), and headache (2 of 10 subjects and 2 of 21 subjects, respectively) and a causal relationship to aliskiren could not be denied for the 3 cases of diarrhoea, but all of these subjects completed the study without requiring particular treatment.

The primary endpoint for this study was hyperplasia score[1)] of mucosal biopsies and at baseline, no subject in either treatment group demonstrated evidence of hyperplasia (score ≥ 2) in any of the regions examined (caecum, ascending colon, descending colon, rectum). There were no subjects in the aliskiren treated group that developed hyperplasia. One subject in the placebo group was observed to exhibit hyperplasia in the rectum following treatment. Two subjects in the aliskiren treated group had a hyperplasia score of 1, both at baseline with values of 0. Another primary endpoint was a mitosis score[2)] and baseline values for mitosis scores were comparable between the treatment groups and no subject in either group demonstrated an increase in mitotic activity following treatment in any of the regions examined.

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

4.(iii).B.(1) Clinical positioning and indication of aliskiren

PMDA asked the applicant to compare the mode of action and the efficacy and safety profiles between aliskiren and other RAS inhibitors and explain the advantages and disadvantages of aliskiren and the characteristics of the patient population for which aliskiren is especially recommended.

The applicant responded as follows:

ACE inhibitors and ARB suppress the RAS by inhibiting the ACE, i.e., an enzyme converting Ang I to Ang II, and by selectively blocking the Ang II type 1 (AT_1) receptor, respectively. However, as ACE inhibitors do not inhibit Ang II production via chymase or other non-ACE pathways, Ang II production is not completely blocked and the escape phenomenon (increases in plasma Ang II in patients treated with long-term ACE inhibitors) has also been reported (Biollaz J et al. *J Cardiovasc Pharmacol.* 1982;4: 966-72). Because ARB blocks the binding of Ang II to the AT_1 receptor, plasma Ang II concentrations are increased. In addition, since ACE inhibitors and ARB both induce a compensatory increase in plasma renin concentration accompanied by increased levels of PRA, full suppression of the RAS cannot be achieved. On the other hand, aliskiren can suppress the entire RAS by inhibiting renin, the enzyme responsible for the first step of the RAS cascade, decreasing PRA despite an increase in plasma renin concentration, and reliably reducing the production of Ang I and all subsequent angiotensin peptides, especially Ang II.

As to the efficacy profile, the blood pressure lowering effect of aliskiren was comparable to that of losartan (ARB) in Japanese Study 1301; a previous clinical study has demonstrated the non-inferiority of the efficacy of ARB that is currently marketed in Japan vs. enalapril, an ACE inhibitor; and foreign clinical

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1) Hyperplasia Score
0 No increase in crypt length (< 0.5 mm)
1 Increase of crypt length (≥ 0.5 mm), without loss of goblet cells or appearance of nuclear crowding
2 Increase of crypt length (≥ 0.5 mm) plus loss of goblet cells or appearance of nuclear crowding
3 Increase of crypt length (≥ 0.5 mm) plus loss of goblet cells and appearance of nuclear crowding as well as superficial serrations, crypt budding, or bifurcations

2) Mitosis Score
0 ≤ 2 mitotic figures in basal 1/2 of 5 consecutive crypts
1 3-4 mitotic figures in basal 1/2 of 5 consecutive crypts
2 Any mitotic figures in superficial 1/2 of 5 consecutive crypts
3 ≥ 5 Mitotic figures in 5 consecutive crypts

studies (Studies 2201, 2203, 2327, 2306, 2307) showed that the blood pressure lowering effect of aliskiren was similar to that of ARB or ACE inhibitor. Based on these findings, the blood pressure lowering effect of aliskiren is considered comparable to that of ARB or ACE inhibitor.

As to the safety profile, in Japanese Study 1301, the incidence of adverse events was 50.3% in the aliskiren 150 mg group, 42.3% in the placebo group, and 46.5% in the losartan 50 mg group and the nature of adverse events was similar across the groups, confirming that the safety of aliskiren is comparable to that of losartan. In foreign clinical studies (foreign subjects in Studies 2201, 2203, 2204, 2327, 2328, 2303, 2304, 2305, 2307, 2309, and 2324), the incidence of adverse events was comparable in all treatment groups, i.e. 35.9% (1351 of 3765 subjects) in the aliskiren alone group, 35.4% (271 of 766 subjects) in the ARB group, and 31.9% (132 of 414 subjects) in the ACE inhibitor group and the nature of adverse events was similar across the groups, except for cough reported frequently with ACE inhibitor.

Regarding the patient population for which aliskiren is especially recommended, since Japanese and foreign clinical studies have confirmed that aliskiren is effective and safe in not only patients with mild to severe essential hypertension but also hypertensive patients with renal impairment or diabetes mellitus and elderly hypertensive patients, as with ARB or ACE inhibitors, aliskiren can be recommended for a broad range of patient populations. In foreign clinical studies, co-administration of an antihypertensive diuretic (Study 2204), Ca antagonist (Study 2305), ARB (Studies 2203 and 2327), or ACE inhibitor (Study 2307) with aliskiren provided additional blood pressure reductions. Thus, the concomitant use of aliskiren is useful for patients with inadequate blood pressure control on a single antihypertensive agent of a different class, for whom aliskiren should be recommended. Furthermore, switching to aliskiren with a different mode of action may be useful for patients unresponsive to other antihypertensive agents of different classes.

PMDA considers as follows:
While aliskiren is similar to other RAS inhibitors in terms of exerting its antihypertensive effect by inhibiting the RAS, there are some differences between the effects of aliskiren and other RAS inhibitors. The differences include the following: (1) aliskiren decreases PRA but increases plasma renin concentration and does not inhibit prorenin receptor activation (Schefe JH et al. *J Hypertens.* 2008;26:1787-94); (2) like ARB, aliskiren have no mechanism via bradykinin as seen with ACE inhibitors; and (3) aliskiren is different from ARB in terms of Ang II action mediated by the Ang II type 2 (AT_2) receptor. In this way, since aliskiren is an antihypertensive agent with a novel mode of action different from other RAS inhibitors and has been recently approved overseas, it is hard to say that its clinical positioning has been established. In addition, it cannot be ruled out that the risk of diarrhoea etc. anticipated from Japanese and foreign clinical study data may be unique to aliskiren among RAS inhibitors, and the risk of colorectal hyperplasia associated with aliskiren cannot be excluded. Therefore, it is necessary to continue to collect sufficient information after the market launch. However, Japanese Study 1301 has demonstrated the non-inferiority of the efficacy of aliskiren 150 mg vs. losartan 50 mg and from a safety point of view, the incidence of adverse events was similar between aliskiren 150 mg and losartan

50 mg. Other safety information was also largely the same as anticipated from the results with existing RAS inhibitors. Based on these findings, aliskiren can be administered as an initial therapy for hypertension. The positioning of aliskiren in the treatment of hypertension will be established with the accumulation of future clinical experience and clinical study data etc. According to currently available information, there is no reason to restrict the use of aliskiren as an initial therapy or in combination with other agents or switching from other agents to aliskiren in the treatment of hypertension. Thus, it is concluded that the proposed indication of "hypertension" is appropriate. A final decision on the appropriateness of the above conclusion etc. will be made, taking also account of comments raised in the Expert Discussion.

4.(iii).B.(2) Efficacy and dosage and administration

4.(iii).B.(2).1) Dosing instruction

(a) Justification for once-daily administration without regard to meals

The applicant explained about the frequency of administration of aliskiren as follows:

Japanese Study 1101 showed that the mean $t_{1/2}$ of aliskiren 75 to 300 mg were 32.5 to 37.0 hours and Japanese Study 1301 demonstrated the non-inferiority of the blood pressure lowering effect of once-daily aliskiren to losartan, which has been approved for a once-daily regimen. In Foreign Studies 2308 and 2324, ABPM data indicated that the blood pressure T/P ratio was ≥ 0.5 as suggested by the "Principles for Clinical Evaluation of New Antihypertensive Drugs" (PFSB/ELD Notification No. 0128001 dated January 28, 2002)." Moreover, a long-term treatment study of aliskiren (Japanese Study 1202) demonstrated a stable antihypertensive effect over a long period of time. Based on the above, it has been determined that aliskiren should be administered once daily.

The applicant explained about the timing of dosing relative to meals as follows:

The difference in msDBP change between the aliskiren 150 mg and placebo groups was comparable between Japanese Study 1201 in which the study drug was administered 30 minutes before a meal and Japanese Study 1301 in which the study drug was administered without regard to meals and the incidence of adverse events in the aliskiren 150 mg group was also similar between Japanese Studies 1201 and 1301. Also, the antihypertensive effect of aliskiren 150 and 300 mg was shown in Japanese Study 1104 in which the study drug was administered 30 minutes after breakfast. Therefore, it has been suggested that the timing of dosing relative to meals has no major impact on the efficacy and safety of aliskiren within the proposed dose range and there is no need to limit the timing of taking aliskiren to before or after a meal.

PMDA considers as follows:

Based on clinical study data, there is no problem with a once daily regimen of aliskiren. Food effect is clinically important information because changing a relation of administration to meals as well as changing the dose affects the efficacy and safety of aliskiren [see "4.(i).B.(2) Food effect"]. The details of a caution statement about food effect, including where it should be stated in the package insert, will be finalized, taking also account of comments raised in the Expert Discussion.

4.(iii).B.(2).2) Dose

(a) Effective dose of aliskiren

The applicant explained about the effective dose of aliskiren as follows:

In Japanese Study 1201, the change in msDBP was -3.2 ± 7.8 mmHg (mean ± SD) in the placebo group, -7.2 ± 7.1 mmHg in the aliskiren 75 mg group, -7.7 ± 8.8 mmHg in the aliskiren 150 mg group, and -10.7 ± 8.8 mmHg in the aliskiren 300 mg group and the absolute change increased with increasing dose. Blood pressure in the aliskiren 150 and 300 mg groups remained stable throughout the treatment period. In Japanese Study 1301, the change in msDBP in the aliskiren 150 mg group was -8.9 ± 9.43 mmHg, showing a superior antihypertensive effect over placebo (-3.0 ± 8.18 mmHg) and the non-inferiority of aliskiren to the control drug, losartan 50 mg (-8.7 ± 8.02 mmHg), was demonstrated. Therefore, the efficacy of aliskiren as an antihypertensive agent has been demonstrated. Furthermore, in foreign placebo-controlled studies (Studies 2201, 2203, 2204, 2308, 2327, 2328), the antihypertensive effect of both aliskiren 150 and 300 mg was significantly superior to that of placebo consistently, but the antihypertensive effect of 75 mg was smaller than those of 150 and 300 mg and there was no significant difference between aliskiren 75 mg and placebo. There were no major differences in the antihypertensive effect between aliskiren 300 mg and 600 mg. Thus, only two doses of 150 and 300 mg were approved in the US and the EU. The above results indicate that aliskiren stably exerts a clinically useful antihypertensive effect at doses ≥ 150 mg and that the effect is peaked at 300 mg. Consequently, it has been determined that the appropriate effective doses of aliskiren for Japanese patients with hypertension are 150 and 300 mg.

PMDA considers as follows:

Japanese clinical studies have demonstrated the efficacy and safety of aliskiren 150 mg and it is appropriate to choose 150 mg as the usual dose. Aliskiren 300 mg as the maximum dose is judged acceptable based on the following findings: Japanese Study 1201 indicated that aliskiren 300 mg is expected to produce a greater blood pressure lowering effect than 150 mg and the incidence of adverse events was almost comparable between aliskiren 150 and 300 mg. The incidence of diarrhoea, which is considered to be a noteworthy adverse event associated with aliskiren, tended to increase in a dose-dependent manner in Japanese Study 1201, but the incidence of diarrhoea in the aliskiren 300 mg group in Japanese Study 1201 was 3.5% (4 of 113 subjects) and the incidence of diarrhoea in subjects on aliskiren 300 mg in Japanese Study 1202 was 2.2% (4 of 184 subjects). Moreover, 155 of 299 subjects were on aliskiren 300 mg at Week 52 in a long-term treatment study 1202, indicating that 300 mg of aliskiren could be used continuously. In Japanese Studies 1303 and 1304, the dose was increased to 300 mg in approximately 70% to 80% of the patients in whom a greater blood pressure lowering effect was achieved by the dose increase, even though aliskiren 150 mg had not been sufficiently effective in those patients. The dosage and dose regimen of aliskiren, including the appropriateness of the above conclusion and the necessity of dose reduction as appropriate [see the next section “(b) 75 mg (dose reduction as appropriate)”], will be determined, taking also account of comments raised in the Expert Discussion.

(b) 75 mg (dose reduction as appropriate)

Aliskiren 75-mg tablet was proposed for registration and according to the Dosage and Administration section of the proposed package insert, the dose may be reduced as appropriate. The applicant explained about the usefulness of aliskiren 75 mg as follows:

In Japanese and foreign clinical studies, the exposure of aliskiren tended to increase in patients with renal impairment and the elderly, but there were no safety problems. Thus, it was thought that even if the usual dose of 150 mg of aliskiren was administered to a broad range of patient populations, the safety would be ensured. However, when establishing the dosage and dose regimen in Japan, we considered that risks and benefits can be more optimized by starting aliskiren at half the usual dose under certain circumstances and that it is useful to include a choice of 75 mg as a reduced dose or an initial dose, taking into account that the package inserts for many of antihypertensive agents marketed in Japan state that the dosage may be "adjusted as appropriate" at the discretion of the doctor and that there are a broad range of patients in clinical practice.

Despite the fact that the absorption of aliskiren is substantially reduced when administered after a meal [see "4.(i).B.(2) Food effect"], the efficacy of aliskiren 75 mg has been demonstrated only in Japanese Study 1201 in which the study drug was administered before a meal and the time course of blood pressure response in the aliskiren 75 mg group was rather unstable compared to those in the aliskiren 150 and 300 mg groups in Japanese Study 1201. Therefore, PMDA asked the applicant to explain whether the efficacy of aliskiren 75 mg can be assured even in fed patients.

The applicant responded as follows:

The cause of an unstable time course of blood pressure response with aliskiren 75 mg in Japanese Study 1201 was discussed, taking account of the relationship between aliskiren blood concentration and PRA and the relationship between PRA and blood pressure. As a result, it was considered that at a low dose of aliskiren, plasma concentrations may be decreased due to food effect or other factors affecting the pharmacokinetics of aliskiren, resulting in inadequate PRA reductions and an unstable antihypertensive effect. Higher PRA over time is anticipated after aliskiren 75 mg compared to 150 and 300 mg. Although blood pressure was reduced in some of the patients in the aliskiren 75 mg group, its blood pressure lowering effect was unstable compared to those of 150 and 300 mg that exhibit more potent PRA inhibitory effects. Thus, the efficacy of 75 mg has not been confirmed. The anticipated patient populations for which a starting dose of 75 mg or dose reduction to 75 mg could be recommended include patients with severe renal impairment (serum creatinine $\geq$ 3.0 mg/dL or CCr < 30 mL/min), very old patients aged $\geq$ 90 years, patients with apparently low body fluid volume or sodium status, and patients with very low body weight. The safety of aliskiren in patient populations close to the above-mentioned populations (renal impairment patients with serum creatinine < 3.0 mg/dL, elderly patients aged $\geq$ 75 years, patients co-administered HCTZ 25 mg, patients who weighed less than 50 kg) was examined among the patients enrolled into Japanese and foreign clinical studies. As a result, there were no safety problems in any of these populations. Thus, it was considered that the usual dose of 150 mg of aliskiren can be administered to a broad range of patient populations, including these special populations. Furthermore, from a safety

point of view, the Careful Administration or Important Precautions section of the proposed package insert cautions that aliskiren should be used carefully in special populations in consideration of the patient's symptoms and condition. Therefore, it has been determined that aliskiren can be used appropriately without a clinical dose of 75 mg and it has been decided to change the proposed Dosage and Administration section to "Usually for adult dose, 150 mg of aliskiren is orally administered once daily. However, the dose may be escalated up to 300 mg if there is lack of efficacy." At the same time, the withdrawal of the application for aliskiren 75-mg tablets has been decided.

PMDA considers as follows:
The applicant claimed that aliskiren 150 mg can be used without problems in many patients as there were no safety problems in special populations, e.g., patients with severe renal impairment, elderly patients aged ≥ 75 years, patients with apparently low body fluid volume or sodium status (concomitant use of HCTZ 25 mg), and low-body-weight patients (< 50 kg), in Japanese and foreign clinical studies. However, it is envisaged that in clinical practice, aliskiren is administered to a broader range of patients than those enrolled into the clinical studies and especially, patients with complex risk factors that have been examined by the applicant in discussion, may require a lower starting dose of aliskiren. Furthermore, aliskiren is characterized by its low BA and its absorption affected by food. There is also a risk of drug-drug interactions, for example, aliskiren plasma concentrations were increased by co-administration of cyclosporine or atorvastatin. Therefore, including a choice of the 75-mg dose of aliskiren in the proposed dosages will enable titration within the low-dose range, thereby making aliskiren more useful as an antihypertensive agent which can be used safely.

Based on the above, PMDA instructed the applicant to re-examine the necessity of offering the 75-mg dose of aliskiren to clinical practice.

The applicant responded as follows:
In response to PMDA's instruction, the necessity of offering the 75-mg dose of aliskiren to clinical practice was re-examined. Even when the exposure of aliskiren may be increased, unless aliskiren is co-administered with a very potent P-glycoprotein inhibitor, such as cyclosporine, which has already been listed in the Precautions for Concomitant Use section of the proposed package insert, the exposure of aliskiren at 150 mg does not exceed the maximum exposure at 300 mg and the safety of aliskiren within the clinical dose range of 150 to 300 mg has been confirmed. Thus, the exposure variability at 150 mg is unlikely to raise a safety concern. In a Japanese long-term treatment study, about 1/4 of the subjects (95 subjects) were treated with aliskiren 75 mg until the end of the study. Meanwhile, in Japanese and foreign clinical studies, the antihypertensive effect of aliskiren 75 mg was unstable compared to that of 150 or 300 mg and the safety of 150 mg, including the incidence of hypotension, was comparable to that of placebo. Therefore, there seems no need to use 75 mg according to the degree of blood pressure control and it has been concluded that offering 75 mg to clinical practice has little significance.

As shown in the above, even when the relationship of the variability in aliskiren plasma concentration at 150 mg with the efficacy and safety of aliskiren is taken into consideration, it is still concluded that a clinical dose of 75 mg has little significance. Even if 75 mg is not made available in clinical practice, 150 mg of aliskiren can be used safely in a broad range of patients.

Taking account of the applicant's conclusion, PMDA considers as follows, regarding the decision not to include a choice of the 75-mg dose of aliskiren in the proposed dosages:
In light of the presence of a broad range of hypertensive patients including those with factors increasing the exposure of aliskiren, a choice of the 75-mg dose of aliskiren is preferable, particularly from a safety standpoint. Meanwhile, Japanese clinical studies have demonstrated the efficacy and safety of aliskiren 150 and 300 mg, aliskiren 150 mg as a starting dose was administered safely to many patients in a Japanese phase III study, and the antihypertensive effect of 75 mg administered after a meal has not been assured. Based on a comprehensive review of these findings, aliskiren with a dose range of 150 to 300 mg may be approved as an antihypertensive agent. However, if there is no choice of the 75-mg dose, it will be necessary to provide cautions. Especially, cautions about ensuring the safety when co-administered with a drug that results in increased plasma concentrations of aliskiren due to drug interactions [see "4.(ii).B.(2) Drug interactions"] and the safety in special populations, e.g., patients with renal impairment, including the appropriateness of the use of aliskiren, will be carefully reviewed in the next item "4.(iii).B.(3) Safety."
A final decision on whether to include a choice of the aliskiren 75 mg dose in the proposed dosages will be made, taking also account of comments raised in the Expert Discussion.

4.(iii).B.(3) Safety

Based on Japanese and foreign clinical study data, the applicant listed diarrhoea, hemoglobin and hematocrit decreased, rash, angioedema, and hyperkalaemia as the important identified risks of aliskiren (increased adverse events or laboratory changes associated with aliskiren) and colorectal hyperplasia, peripheral oedema, hypotension, and renal impairment as the important potential risks of aliskiren though their relationship to aliskiren has not been identified.

Among these risks, major risks or risks that cannot be predicted from other RAS inhibitors or other antihypertensive agents include hyperkalaemia, diarrhoea and colorectal hyperplasia, and angioedema. Among the intended special populations, patients with renal impairment and elderly patients were considered to need special care, based on Japanese clinical study data. These safety issues and the appropriateness of the use of aliskiren during pregnancy, which is considered to be a common problem among RAS inhibitors, will be described in details below.

4.(iii).B.(3).1) Hyperkalaemia

PMDA asked the applicant to scrutinize the background of subjects with increases in serum K > 5.0 mEq/L in Japanese and foreign clinical studies and determine the risk factors for increases in serum K.

The applicant responded as follows:

Based on the data from Japanese short-term placebo-controlled studies (Studies 1201 and 1301), a Japanese long-term open-label study (Study 1202), a Japanese study in hypertensive patients with renal impairment (Study 1303), a Japanese study in patients with severe hypertension (Study 1304), and foreign short-term placebo-controlled studies, the proportions of subjects with increases in serum K > 5.0 mEq/L following treatment with aliskiren by background factors, i.e. age (< 65 years, ≥ 65 years), gender, renal function (estimated glomerular filtration rate [eGFR], < 60 mL/min/1.73 m^2, ≥ 60 mL/min/1.73 m^2), diabetic status, and baseline serum K (≤ 4.5 mEq/L, > 4.5 mEq/L), were determined and the influences of complications and concomitant medications during the study period were also examined.

As a result, the incidence of hyperkalaemia tended to be higher in the following categories of subjects: ≥ 65 years of age; eGFR < 60 mL/min/1.73m^2; high baseline serum K; and concomitant use of ARB. As to age, the incidence of increases in serum K > 5.0 mEq/L was higher in aliskiren-treated subjects aged ≥ 65 years (Studies 1201 and 1301 combined, subjects treated with aliskiren alone, < 65 years of age, 4.5% [25 of 555 subjects], ≥ 65 years of age, 11.5% [10 of 87 subjects]; Study 1202, aliskiren-treated subjects, < 65 years of age, 8.2% [25 of 305 subjects], ≥ 65 years of age, 15.4% [6 of 39 subjects]), but there were no major differences in the incidence from placebo-treated subjects (Studies 1201 and 1301 combined, < 65 years of age, 3.3% [8 of 242 subjects], ≥ 65 years of age, 7.7% [2 of 26 subjects]). As to renal function, in Japanese Study 1303 involving patients with renal impairment, the incidence of increases in serum K > 5.0 mEq/L following treatment with aliskiren was 32.5% (13 of 40 subjects). As to baseline serum K, in Japanese short-term placebo-controlled studies, the incidence of increases in serum K > 5.0 mEq/L following treatment with aliskiren was 19.5% (22 of 113 subjects) in subjects with baseline serum K > 4.5 mEq/L, which was higher than 2.5% (13 of 529 subjects) in subjects with baseline serum K ≤ 4.5 mEq/L. As to the concomitant use of ARB, in foreign short-term placebo-controlled studies, the incidence of increases in serum K > 5.0 mEq/L was 14.5% (85 of 588 subjects) in the concomitant ARB subgroup, which was higher than 7.4% (195 of 2652 subjects) in the aliskiren alone subgroup. Many of the patients with renal impairment had high baseline serum K values and it was likely that a large variability in serum K resulted in a high incidence of increases in serum K > 5.0 mEq/L following the administration of aliskiren. On the other hand, there was no consistent trend regarding complications or concomitant medications. The above results indicate that although the risk of increases in serum K associated with aliskiren is small, serum K is likely to exceed 5.0 mEq/L following the administration of aliskiren in patients with high serum K values, patients with renal impairment, and patients co-administered ARB. Also, foreign clinical studies suggest that serum K is likely to increase in patients co-administered ACE inhibitor.

PMDA considers as follows:

There is a concern that aliskiren that inhibits the RAS would result in increased serum K values. According to pooled analysis of Japanese clinical studies, the incidence of increases in serum K > 5.0 mEq/L was 4.8% (20 of 414 subjects) in the aliskiren 150 mg group and 8.8% (10 of 113 subjects) in the aliskiren 300 mg group, which tended to be higher than that in the losartan control group (4.0% [12 of 302 subjects]). Taking account of these findings, it is necessary to appropriately caution about serum K values following

the administration of aliskiren. The applicant listed ≥ 65 years of age, high baseline serum K, low eGFR, and concomitant use of ARB as the risk factors for increases in serum K associated with aliskiren and caution is needed for all of these factors. However, these risk factors have been identified with other RAS inhibitors as well and there have been no clinical study data indicating that the safety of aliskiren is markedly inferior to that of other RAS inhibitors. As in the cases of these approved drugs, it is appropriate to take the following measures: Careful administration of aliskiren is recommended in patients with hyperkalaemia and those with serious renal impairment, and the proposed package insert should caution about patients co-administered RAS inhibitor, those with renal impairment, and those with diabetes mellitus who are likely to have elevated serum K. On the other hand, it is necessary to caution about a high incidence of increases in serum K in the elderly. The details of information to be provided about increases in serum K following the administration of aliskiren will be finalized, taking also account of comments raised in the Expert Discussion.

4.(iii).B.(3).2) Diarrhoea

As discussed in "4.(iii).B.(2) 2) (a) Effective dose of aliskiren," clinical study data suggested that high-dose aliskiren may increase the risk of diarrhoea. PMDA asked the applicant to explain its cause in terms of both blood concentrations and direct exposure of the gastrointestinal tract to aliskiren.

The applicant responded as follows:

Diarrhoea observed in clinical studies was inferred to be a change associated with the pharmacological effects of aliskiren on the RAS. The RAS is involved in the transport of water and electrolytes in the small intestine and Ang II induces re-absorption of Na and water via the AT_2 receptor and secretion of them via the AT_1 receptor. Thus, transport of Na and water across the intestinal epithelium is thought to depend on the relative activation of the AT_2 and AT_1 receptors.

Concerning plasma aliskiren concentrations, 3 subjects experienced diarrhoea in Japanese Study 1301 and 2 of them had trough plasma aliskiren concentrations that were lower than the mean concentration and there was no trend towards an association between plasma aliskiren concentration and the development of diarrhoea. In Foreign Study 2103, the mucosal concentrations in 3 subjects with diarrhoea were lower than the mean concentration of all subjects, but mucosal specimens at the onset of the event were not collected and the effects of direct exposure to aliskiren that stayed in the gastrointestinal tract were unknown.

PMDA considers as follows:

Taking into account that the mode of action of aliskiren is PRA inhibition, decreasing Ang II production, the applicant's response that the mechanism of the development of diarrhoea is the relative activation of the AT_2 and AT_1 receptors is not convincing. Since the association between aliskiren blood concentrations and diarrhoea or between aliskiren gastrointestinal concentrations and diarrhoea has not been clarified, diarrhoea may develop at any dose. Diarrhoea is listed as "having an incidence of ≥ 1%" in the "Other adverse reactions" section of the proposed package insert and this caution is appropriate in light of the level of its seriousness as an adverse drug reaction. However, if an adverse reaction of diarrhoea is more

characteristic of aliskiren than other RAS inhibitors, it is necessary to consider appropriate measures to provide information before introducing aliskiren to clinical practice. A final decision on the appropriateness of the above conclusion will be made, taking also account of comments raised in the Expert Discussion.

4.(iii).B.(3).3) Colorectal hyperplasia

Since non-clinical study data suggested that colorectal hyperplasia may develop following the administration of high-dose aliskiren, PMDA asked the applicant to discuss its cause in terms of both blood concentrations and direct exposure of the gastrointestinal tract to aliskiren and furthermore, consider post-marketing safety measures as needed.

The applicant responded as follows:

With respect to colorectal hyperplasia, in a mechanistic study in rats, mucosal hyperplasia in the cecum and colon was observed after 3 days of treatment with aliskiren admixed with the diet, which was reversible upon drug withdrawal. In 1-week and 4-week repeat-dose mechanistic studies, toxicogenomic analysis was performed. As a result, gene expression changes in the jejunum, ileum, cecum, and colon were largely consistent with histological changes and changes in the lower gastrointestinal tract following treatment with aliskiren were inferred to be toxic injury to the mucosal epithelium, triggering an inflammatory reaction to local irritation caused by aliskiren and an epithelial reaction resulting in the induction of cell proliferation and growth factors. Proliferative changes in the gastrointestinal tract were not noted in marmosets in a long-term repeat-dose toxicity study or in humans treated with the proposed highest clinical dose of aliskiren (300 mg) for 8 weeks, indicating that there are species differences in the development of mucosal lesions in the lower gastrointestinal tract associated with aliskiren, which was noted in the rodent. Aliskiren is a non-genotoxic substance and it is generally understood that thresholds exist for the carcinogenicity of non-genotoxic substances.

Fecal aliskiren concentrations and tissue aliskiren concentrations in the jejunum, ileum, cecum, and colon in rats following the administration of the NOAEL dose of aliskiren for a carcinogenicity study, i.e., 276 mg/kg/day, were compared to fecal and gastrointestinal tissue aliskiren concentrations in humans following the administration of aliskiren 300 mg. As a result, there were 7- to 11-fold and 6-fold safety margins based on fecal and gastrointestinal tissue concentrations, respectively. An *in vitro* study using rat isolated colon preparations suggested that rat tissue may be more sensitive to the local irritant effects of aliskiren than human tissue, which indicated that the true safety margin in humans is even wider. At the highest doses in 13- and 39-week repeat-dose toxicity studies in marmosets, fecal aliskiren concentrations were up to 12-fold higher than those in humans, but there were no aliskiren-related histological changes in the gastrointestinal tract, which also supports the safety of aliskiren in humans.

Because colorectal hyperplasia was not reported in Japanese clinical studies assessing the pharmacokinetics of aliskiren, the association between plasma aliskiren concentrations and colorectal hyperplasia within the dose range of 75 to 300 mg is unknown.

As to the future plan for information collection, since it was pointed out at the time of the US approval that the effects of long-term treatment with aliskiren on the gastrointestinal tract need to be further scrutinized, it was planned to collect detailed information on gastrointestinal symptoms and investigate the effects of long-term treatment with aliskiren on the gastrointestinal tract via post-marketing clinical studies and large-scale clinical studies overseas. Also in Japan, it is planned to continuously collect information after the market launch. Japanese data are currently being collected from large-scale clinical studies that are ongoing in Japan and overseas to assess the organ protective effects of aliskiren. Based on the obtained information including these data, necessary actions will be considered.

PMDA considers as follows:
Although the association between plasma aliskiren concentrations and colorectal hyperplasia or between gastrointestinal aliskiren concentrations and colorectal hyperplasia has not been clarified, the incidence of this event in clinical studies is low and its clinical impact is unknown. At present, it should be noted that this event may be unique to aliskiren, but colorectal hyperplasia will not become a clinically relevant problem. On the other hand, the short-term safety of aliskiren regarding the induction of colorectal hyperplasia has been confirmed by endoscopy and biopsy in Foreign Study 2103, while safety information on long-term treatment is limited. Thus, post-marketing surveillance needs to be planned so as to collect gastrointestinal adverse events appropriately. Furthermore, taking also account of future safety information obtained from Japanese and foreign clinical studies, the necessity of new safety measures should be considered as required.

A final decision on the details of information to be provided about colorectal hyperplasia and the appropriateness of the post-marketing surveillance plan to collect information will be made, taking also account of comments raised in the Expert Discussion.

4.(iii).B.(3).4) Angioedema

The applicant explained about angioedema, which is one of adverse drug reactions that may occur associated with drugs acting on the RAS, as follows:
While the development of angioedema has been suggested to be mainly related to kininase II inhibition by ACE inhibitors (Vleeming W et al. *Drug Saf.* 1998;18:171-88), it has also been reported that angioedema recurred following the administration of ARB that does not inhibit kininase II in patients with ACE inhibitor-induced angioedema (Dykewicz MS. *Curr Opin Allergy Clin Immunol.* 2004;4: 267-70). Thus, it cannot be ruled out that aliskiren may cause angioedema. However, angioedema-related adverse events (angioedema, face or pharyngeal edema) were not reported in any of Japanese clinical studies (including Japanese subjects in Study 2324). Based on all foreign clinical studies included in pooled analyses (a total of 17 studies including 15 studies completed by December 31, 2006 among 18 foreign clinical studies submitted as the reference data and Foreign Study 2308 and Foreign Study 2324 [the data from foreign subjects who participated in the study] submitted as the evaluation data), the incidence of angioedema-related adverse events was < 0.1% in all subjects treated with aliskiren. A serious adverse

event of angioedema occurred in 2 subjects in the aliskiren group and a causal relationship to the study drug could not be denied for both cases, but the event resolved within a short period of time (11 and 6 days, respectively) following study drug discontinuation or symptomatic treatment. Furthermore, angioedema-related adverse events did not occur at a high frequency in the aliskiren group and the incidence was not increased with increasing dose of aliskiren, co-administration of other antihypertensive agents, or prolonged treatment. The above results indicate that the risk of angioedema associated with aliskiren is small.

PMDA considers as follows:
The applicant's explanation is largely appropriate. However, the following action was taken on February 19, 2009, after the approval of aliskiren in the EU. The European Medicines Agency recommended adding a contraindication to the Product Information for aliskiren, stating that it must not be used in patients who have experienced angioedema (swelling of the tissues beneath the skin) when taking aliskiren in the past. The Agency also recommended the inclusion of a warning, stating that patients who develop signs of angioedema should stop treatment and seek medical attention. Based also on these recommendations, it is necessary to appropriately provide information on the risk of angioedema associated with aliskiren. The details of a caution statement about the risk of angioedema associated with aliskiren in the proposed package insert will be finalized, taking also account of comments raised in the Expert Discussion.

4.(iii).B.(3).5) Use in patients with renal impairment

The applicant explained about the use of aliskiren in patients with renal impairment as follows:
In Japanese Study 1303 involving Japanese hypertensive patients with mild to moderate renal impairment, trough plasma aliskiren concentrations tended to increase with decreasing renal function. Meanwhile, the antihypertensive effects of 75 to 300 mg of aliskiren in Japanese Study 1303 were comparable to those in patients with essential hypertension who have normal renal function in a dose-finding study (Japanese Study 1201) and a confirmatory study (Japanese Study 1301). Also, regarding safety, even though the exposure of aliskiren increased with decreasing renal function, there were no major differences in the incidence of adverse events. In Foreign Study 2209, the pharmacokinetics of aliskiren in patients with mild to severe renal impairment were compared with those in gender-, race-, age-, and body weight-matched healthy subjects with normal renal function. As a result, although the exposure in renally impaired patients tended to be higher than in healthy subjects, the exposure did not show a correlation with the severity of renal impairment. The above results indicate that decreased renal function has no major impact on the efficacy and safety of aliskiren.

PMDA considers as follows:
As discussed in "4.(iii).B.(3).1) Hyperkalaemia," careful administration of aliskiren should be recommended in renally impaired patients with serum creatinine < 3.0 mg/dL since the incidence of hyperkalaemia exceeded 30%. Even if serum creatinine is less than 3.0 mg/dL, based on the equation to estimate GFR for Japanese (eGFR [men] = 194 × serum creatinine value$^{-1.094}$ × age$^{-0.287}$, eGFR [women] = eGFR [men] × 0.739), there should be many patients classified as CKD stage 4 or greater. Because the

renal function is likely to deteriorate with decreasing blood pressure in patients with serious renal impairment, which may lead to a vicious circle of further deterioration of the renal function, careful administration is recommended in the package insert also for antihypertensive agents other than RAS inhibitors. In light of these points etc., a caution statement that aliskiren should be administered with care in patients with serum creatinine ≥ 3.0 mg/dL is inadequate and aliskiren should be administered with care in all patients with decreased renal function, not limited to those with serum creatinine ≥ 3.0 mg/dL. A final decision on the appropriateness of the above conclusion will be made, taking also account of comments raised in the Expert Discussion.

4.(iii).B.(3).6) Use in the elderly

The applicant explained about the use of aliskiren in the elderly as follows:

In Foreign Study 2217 assessing the effect of age on the pharmacokinetics of aliskiren in non-elderly (≥ 18 and ≤ 45 years) and elderly (≥ 65 years) subjects, the geometric mean ratios of $AUC_{0\text{-}inf}$ and C_{max} of aliskiren (elderly/non-elderly) were 1.57 and 1.28, respectively. However, in Japanese clinical studies (Japanese Studies 1201 and 1301 combined), the change in msDBP was -8.6 mmHg in subjects aged < 65 years (355 subjects) and -8.3 mmHg in subjects aged ≥ 65 years (59 subjects) at the aliskiren 150 mg dose and -10.7 mmHg in subjects aged < 65 years (103 subjects) and -10.5 mmHg in subjects aged ≥ 65 years (10 subjects) at the aliskiren 300 mg dose. There were no major differences between the age groups. Likewise, there were also no major differences in msSBP change between the age groups. The incidence of adverse events following the administration of aliskiren was 52.8% (293 of 555 subjects) and 44.8% (39 of 87 subjects), respectively, and there were no differences between the age groups. Adverse events reported by at least 2 subjects aged ≥ 65 years were nasopharyngitis (13 of 87 subjects) (14.9%), ALT increased (2 of 87 subjects) (2.3%), AST increased (2 of 87 subjects) (2.3%), and headache (2 of 87 subjects) (2.3%) and the incidences of these events were comparable to those in subjects aged < 65 years. Also in foreign clinical studies, the efficacy and safety of aliskiren were comparable between the age groups. As shown in the above, the efficacy and safety of aliskiren were similar between the elderly and non-elderly populations in Japanese and foreign clinical studies, suggesting that differences in the exposure have no major impact on the clinical effects. Thus, dose adjustment for the elderly was considered unnecessary. However, as the elderly often has reduced physiological function and careful administration is recommended, a general caution statement has been included in “5. Use in the Elderly” of the PRECAUTIONS section in the proposed package insert.

PMDA considers as follows:

Although a rigorous comparison of the efficacy and safety of aliskiren between the elderly and non-elderly cannot be made due to the limited number of elderly patients enrolled into Japanese clinical studies, based on the submitted clinical study data etc., dose adjustment of aliskiren just because of old age is unnecessary. On the other hand, considering that the risk of hyperkalaemia rises in the elderly, it is necessary to caution that aliskiren should be administered with care in the elderly. Also, the “Use in the Elderly” section in the proposed package insert states that “there were no differences in the efficacy and safety of aliskiren between the elderly aged ≥ 65 years and the non-elderly aged < 65 years in clinical

studies." Yet, despite the fact that antihypertensive agents are widely used in this patient population in clinical practice, very few elderly patients aged ≥ 75 years were enrolled into clinical studies, which essentially questions whether this statement is appropriate as the information about a patient population requiring caution in antihypertensive treatment. A final decision on the details and appropriateness of a caution statement about the elderly will be made, taking account of comments raised in the Expert Discussion.

4.(iii).B.(3).7) Use in pregnant women

ACE inhibitors and ARB that have been approved in Japan are contraindicated in pregnant women because oligohydramnios, fetal or neonatal death, neonatal hypotension, renal failure, multi-organ failure, and skull hypoplasia and limb deformation, craniofacial deformation, and hypoplastic lung development presumably associated with oligohydramnios, etc. have been reported in patients treated during the second and third trimesters of pregnancy. Furthermore, the "Use in Pregnant Women etc." section of the package insert cautions that the drug should not be used in pregnant women or in women who may possibly be pregnant and that when pregnancy occurs in a patient using the drug, treatment should be discontinued as soon as possible. On the other hand, according to the package insert proposed by the applicant, aliskiren is contraindicated during the second and third trimesters of pregnancy only while it is stated in the "Use in Pregnant Women etc." section that "aliskiren should not be administered during the first trimester of pregnancy or in women who are planning to become pregnant and when pregnancy occurs in a patient using the drug, treatment should be discontinued as soon as possible," which virtually denying the use of aliskiren in pregnant women, including patients who are found to be in the first trimester of pregnancy. In light of the seriousness of events that potentially occur in fetuses following the administration of similar drugs, taking also into account that aliskiren crosses the placenta, it is inappropriate to provide a caution that is different from that of similar drugs in spite of being aware that the use of aliskiren during pregnancy entails the same risks as those associated with similar drugs. Taking also into account that the first and second trimesters of pregnancy cannot be distinguished rigorously, PMDA considers that aliskiren should be contraindicated in pregnant women. A final decision on the appropriateness of the above conclusion will be made, taking also account of comments raised in the Expert Discussion.

4.(iii).B.(4) Post-marketing surveillance etc.

The applicant explained about a post-marketing surveillance plan for aliskiren as follows:

For post-marketing surveillance, a special drug use-results survey with a planned number of patients of 3000 and a 1-year observation period will be conducted. This survey will focus on the patient background, such as complications and concomitant drugs in hypertensive treatment, and the time courses of serum creatinine and blood urea nitrogen as well as serum K during treatment with aliskiren. If elderly patients, patients with renal impairment, and patients with hepatic impairment are enrolled into this survey, safety and efficacy issues in special populations will be identified. Based on currently available non-clinical and clinical study data, diarrhoea, hemoglobin and hematocrit decreased, rash, angioedema, and hyperkalaemia have been listed as the important identified risks of aliskiren (increased adverse events or laboratory changes associated with aliskiren) and colorectal hyperplasia, peripheral oedema, hypotension, and renal

impairment have been anticipated as the important potential risks of aliskiren though their relationship to aliskiren has not been identified. Therefore, information on these risks will also be collected.

PMDA considers as follows:
It is important to collect information on the efficacy and safety of aliskiren in the elderly aged ≥ 75 years via post-marketing surveillance, as sufficient data concerning this patient population could not be obtained from Japanese clinical studies. Regarding interactions with co-administered drugs, which was a key issue in the review, concrete measures should be taken to collect information on co-administration of other drugs, especially CYP3A4 inhibitors or P-glycoprotein inhibitors, and if possible, information on the patient's pattern for taking aliskiren, i.e., taking after or before a meal, should be collected. The outline of a post-marketing surveillance plan (draft) presented by the applicant is largely appropriate, but the details will be further reviewed, taking also account of comments raised in the Expert Discussion.

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

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

A document-based inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, there were no particular problems. Thus, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted product application documents.

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

GCP on-site inspection took place in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.5.1-1, 5.3.5.1-2, 5.3.5.2-1, 5.3.5.2-2, 5.3.5.2-3). As a result, protocol deviations (the use of prohibited concomitant medications) were found at some clinical trial sites, which had not been detected by the sponsor's monitors. Such findings suggested that monitoring had not been appropriately performed in accordance with the standard operating procedures, but PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted product application documents.

IV. Overall Evaluation

As a result of the review described above, regarding the efficacy of aliskiren, PMDA determined that aliskiren was shown to have an antihypertensive effect that is significantly greater compared to placebo and comparable to losartan. As to safety, there is a concern about gastrointestinal disorders etc. as adverse reactions to aliskiren deserving special attention, on which information should be continuously collected, whereas the nature and incidence etc. of other adverse events associated with aliskiren did not suggest any special concern compared to the safety information on ACE inhibitors and ARB, which are approved antihypertensive agents acting mainly by inhibiting the RAS. Thus, aliskiren was considered tolerable as an antihypertensive drug. As a result, it has been concluded that there are no major problems affecting the

approval decision for aliskiren as long as appropriate cautions are provided. The details of the review result including cautions necessary for offering aliskiren to clinical practice and post-marketing information collection will be finalized, taking account of comments raised in the Expert Discussion.

Review Report (2)

May 21, 2009

I. Product Submitted for Registration

[Brand name]	Rasilez Tablets 150 mg
[Non-proprietary name]	Aliskiren Fumarate
[Applicant]	Novartis Pharma K.K.
[Date of application]	February 29, 2008 (a marketing application for a drug)

II. Content of the Review

PMDA sought the expert advisors' comments based on the Review Report (1). The results of the review, taking account of discussions with the expert advisors, are reported below.

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

(1) Clinical positioning and indication

The following comments were raised from the expert advisors: (1) although aliskiren is a promising antihypertensive agent with a novel mode of action, taking into account that there are many alternative antihypertensive agents, there is no need to hurry to spread the use of aliskiren until experiences on the efficacy and safety of long-term treatment are accumulated; and (2) the advantages and disadvantages of chronic inhibition of renin should be examined over a long period of time, and accordingly post-marketing information is important. Consequently, the expert advisors supported PMDA's view that the positioning of aliskiren in the treatment of hypertension will be established with further accumulation of information in future. Concerning the indication, while there was an opinion from the expert advisors that the appropriate indication for aliskiren is "hypertension," it was commented that most of efficacy studies of aliskiren included patients with essential hypertension and there is insufficient evidence for adding secondary hypertension to the indication. Based on clinical study data and the approval status and usage conditions of similar drugs etc., the effects expected of aliskiren and whether there is "hypertension" for which the use of aliskiren causes a safety concern, etc. were discussed. In the end, on the premise that appropriate patients for the use of aliskiren will be selected in clinical practice, referring also to the indications of existing antihypertensive agents, PMDA's conclusion that the proposed indication of "hypertension" is appropriate was supported by the expert advisors.

(2) Dosage and administration

1) Food effect

The following comments, among others, were raised from the expert advisors: (1) Provided that patients are advised to establish a routine pattern for taking aliskiren with regard to meals, offering aliskiren with a novel mode of action to clinical practice has its significance. (2) While the exposure variability due to food effect could affect the safety of aliskiren, food effect is considered small from an efficacy point of view. (3) If there is a concern about gastrointestinal tract irritation caused by aliskiren, administration after meals may be safer. (4) Food effect on the exposure of aliskiren is evident. Although the dosage and dose regimen was established mainly on the basis of the data from a Japanese phase II study in which the study drug was administered before a meal, the study drug was administered without requiring a fixed relation of administration to meals (before or after a meal) in a Japanese phase III study. Therefore, it is questionable whether it is possible to claim that the Japanese phase III study has confirmed the efficacy and safety of aliskiren 150 mg compared to placebo and losartan 50 mg as controls. (5) Since there remain concerns regarding both efficacy and safety, the relationship of the relation of administration to meals to safety and efficacy should be investigated before approval, not after marketing.

Against the background of these comments, food effect was further discussed. As a result, there was an opinion that provided that patients will basically establish a routine pattern for taking aliskiren with regard to meals, food effect is unlikely to be an issue affecting the approval decision for aliskiren, because the dose of an antihypertensive agent is carefully adjusted after monitoring blood pressure and there were no major problems when aliskiren was initiated at 150 mg before a meal in Japanese clinical studies etc. In the end, the expert advisors supported PMDA's view that as long as it is cautioned that patients should establish a routine pattern for taking aliskiren with regard to meals and that if the timing of taking aliskiren relative to meals is changed, attention should be paid to changes in the symptoms, aliskiren may be offered to clinical practice.

The expert advisors also supported the following opinion by PMDA: "Patients should establish a routine pattern for taking aliskiren with regard to meals" is clinically important information that should be included in the Precautions of Dosage and Administration section and it should be cautioned in the Important Precautions section, etc. that "if the timing of taking aliskiren relative to meals is changed, attention should be paid to changes in the symptoms."

2) Usual dose

The expert advisors supported the following conclusion by PMDA: A Japanese phase III study has demonstrated the efficacy and tolerable safety of aliskiren that support the usual dose of 150 mg of aliskiren and taking also account of Japanese phase II and long-term treatment data etc., 300 mg may be selected as the maximum dose of aliskiren. The expert advisors agreed to caution about very low BA of aliskiren, which contributes to a very large variability in the exposure of aliskiren, and high intra- and inter-individual variability of C_{max} and AUC.

3) Decision not to include the 75-mg dose

As to the dosage and dose regimen of aliskiren, the applicant decided not to offer a choice of the 75-mg dose to clinical practice. Most of the expert advisors commented that based on the clinical study data and pharmacokinetic characteristics of aliskiren, there should be patients who are expected to respond to 75 mg or whose safety cannot be ensured at 150 mg and a choice of the 75-mg dose is needed. In addition to an opinion that withdrawal of the application for 75-mg tablets should not be accepted based on the reason given by the applicant, the following comment was raised: it is also anticipated that patients with decreased renal function cannot be treated safely with 150 mg and if the 75-mg dose cannot be chosen, an additional safety study using a starting dose of 150 mg should be conducted before approval. However, when a review was conducted again based on the assumption that a choice of the 75-mg dose is not included, the expert advisors eventually supported PMDA's conclusion that aliskiren may be offered to clinical practice if the information on the factors affecting the exposure of aliskiren is provided appropriately, though it is undeniable that no choice of a dose lower than 150 mg will increase the number of patients for whom the use of aliskiren is not appropriate.

After the above discussion, the following conclusion by PMDA was supported by the expert advisors in the end: provided that it is cautioned that aliskiren should not be selected for patients for whom a dose lower than 150 mg of aliskiren is considered appropriate, it is acceptable that the proposed Dosage and Administration section states: Usually for adult dose, 150 mg of aliskiren is orally administered once daily. However, the dose may be escalated up to 300 mg if there is lack of efficacy.

Based on the above discussion, PMDA instructed the applicant to modify the proposed package insert and the applicant responded as follows:

It will be stated in the Precautions of Dosage and Administration section that "Because C_{max} and AUC are increased approximately 3.9-fold and approximately 2.2-fold, respectively, after fasted administration of aliskiren compared with fed administration, each patient should establish a routine pattern for taking aliskiren with regard to meals (before or after a meal) and take aliskiren under the same conditions every day, wherever possible" and it will be stated in the Important Precautions section that "Because C_{max} and AUC are increased approximately 3.9-fold and approximately 2.2-fold, respectively, after fasted administration of aliskiren compared with fed administration, if the timing of taking aliskiren relative to meals is changed, particular attention should be paid to changes in the symptoms." and "Because aliskiren has low bioavailability and high inter-individual variability, blood concentrations may exceed those estimated from clinical doses due to various factors. Prior to the use of aliskiren, the individual patient's background should be fully taken into consideration and whether or not the use of aliskiren is appropriate should be determined carefully." Furthermore, it will be added in the Pharmacokinetics section that "The absolute bioavailability of aliskiren was approximately 2% to 3%. In healthy volunteers (fasted administration), the intra-individual coefficient of variation (CV%) was 53% for C_{max} and 34% for AUC and the inter-individual CV% was 76% for C_{max} and 54% for AUC."

PMDA accepted the applicant's response.

(3) Safety

1) Hyperkalaemia

The following conclusion by PMDA was supported by the expert advisors: since the same mechanism of development of hyperkalaemia is assumed for RAS inhibitors and pooled analysis of Japanese clinical studies showed a trend that the incidence of increases in serum K > 5.0 mEq/L was highest in the aliskiren 300 mg group followed by the aliskiren 150 mg group and then the losartan 50 mg group, it is necessary to caution about hyperkalaemia in the same manner as existing ACE inhibitors and ARB. Moreover, it should be added in the package insert that Japanese clinical study data suggested that "old age" is one of the risk factors for increases in serum K.

Based on the above discussion, PMDA instructed the applicant to modify the proposed package insert and the applicant responded that it will be added in "patients with hyperkalaemia" of the Careful Administration section that old age is a risk factor.

PMDA accepted the applicant's response.

2) Colorectal hyperplasia

PMDA made the following conclusion on colorectal hyperplasia, which has been shown to be a potential risk unique to aliskiren in non-clinical studies: this event has not been reported in Japanese clinical studies and its incidences in foreign clinical studies were also low. Thus, at present, although the package insert should caution about colorectal hyperplasia as a noteworthy adverse drug reaction, as long as aliskiren is administered with due attention to its possible occurrence, colorectal hyperplasia will not become a clinically relevant problem. On the other hand, a post-marketing clinical study to assess colorectal hyperplasia is ongoing overseas, and a multinational clinical trial enrolling Japanese subjects will also be conducted in future, though the target disease is different. Therefore, it is necessary to sequentially assess the results from these studies as well as the information obtained via post-marketing surveillance and review the appropriateness of safety measures etc., as needed.

The following comment was raised from the expert advisors: It is not certain that hyperplasia is directly linked to carcinogenesis. Even if a concern about this event is investigated, a long-term, large-scale investigation will be required. Thus, PMDA's suggestion is appropriate as a measure available at the moment.

The expert advisors supported PMDA's conclusion including that on the appropriateness of the information on this event to be collected after the market launch.

3) Angioedema

The appropriateness of a statement regarding a concern about angioedema associated with aliskiren in the proposed package insert was discussed and the expert advisors agreed that the proposed statement is acceptable until additional information becomes available.

4) Use in patients with renal impairment

The following comment was raised from the expert advisors: The applicant's claim that decreased renal function has no major impact on the efficacy and safety of aliskiren because the exposure of aliskiren is increased with decreasing renal function, but there were no major differences in the efficacy of aliskiren or the occurrence of adverse events in Japanese clinical studies etc. is not appropriate. Taking into account that increases in serum K were observed at a high frequency also in renally impaired patients with serum creatinine < 3.0 mg/dL, it is inappropriate to exclude patients with serum creatinine < 3.0 mg/dL from the patient populations to whom aliskiren should be administered with care.

The expert advisors supported PMDA's conclusion that aliskiren should be administered with care in all patients with renal impairment regardless of serum creatinine value.

Based on the above discussion, PMDA instructed the applicant to modify the proposed package insert and the applicant responded that careful administration of aliskiren will be recommended in patients with renal impairment regardless of serum creatinine value.

PMDA accepted the applicant's response.

5) Use in the elderly

The expert advisors supported PMDA's conclusion that taking also account of an increased risk of hyperkalaemia in the elderly etc., aliskiren should be "administered with care" in the elderly, as with existing RAS inhibitors.

Based on the above discussion, PMDA instructed the applicant to modify the proposed package insert and the applicant responded that the package insert will state that careful administration of aliskiren is recommended in the elderly.

PMDA accepted the applicant's response.

6) Drug interactions

Co-administration of cyclosporine resulted in an approximately 5-fold increase in the AUC of aliskiren and co-administration of atorvastatin resulted in an approximately 1.5-fold increase in the AUC of aliskiren. Since a dose of aliskiren lower than 150 mg cannot be chosen, there is a good possibility that due to a 5-fold variability in the exposure, 150 mg results in a higher exposure than 600 mg that is claimed by the applicant to have been tolerated. Many other alternative antihypertensive agents are available. Taking account of these points, PMDA concluded that the concomitant use of aliskiren with cyclosporine should be contraindicated and atorvastatin should be listed in the Precautions for Concomitant Use section. The following comments were raised from the expert advisors: As long as prescribing physicians understand the pharmacokinetic properties of aliskiren and cyclosporine, listing cyclosporine in the Precautions for

Concomitant Use section is acceptable. On the other hand, if ensuring patient safety is more important, the concomitant use of aliskiren with cyclosporine should be contraindicated and atorvastatin should be listed to alert the physicians. In the end, PMDA's conclusion was supported by the expert advisors.

Based on the above discussion, PMDA instructed the applicant to modify the proposed package insert and the applicant responded that the concomitant use of aliskiren with cyclosporine will be contraindicated and atorvastatin will be added in the Precautions for Concomitant Use section.

PMDA accepted the applicant's response.

7) Use in pregnancy

ACE inhibitors and ARB are contraindicated in pregnant women due to a high fetal risk, and the applicant anticipates that aliskiren has similar risks to ACE inhibitors and ARB. Also, animal experiments revealed that aliskiren crosses the placenta. Based on these facts, PMDA concluded that aliskiren should be contraindicated in pregnant women, etc. The expert advisors supported this conclusion by PMDA.

Based on the above discussion, PMDA instructed the applicant to modify the proposed package insert and the applicant responded that aliskiren will be contraindicated in pregnant women or in women who may possibly be pregnant.

PMDA accepted the applicant's response.

(4) Post-marketing surveillance etc.

The expert advisors raised the following comments on the outline of a plan of a special drug use-results survey with a planned number of patients of 3000 and a 1-year observation period, which had been submitted by the applicant: (1) Although aliskiren is expected to be administered to a broad range of hypertensive patients over a long period of time after the market launch, the influence of an unprecedented upstream inhibition of the RAS over a long period of time and the effects of complications arising during the long-term course of individual patients and therapeutic drugs for these complications on the efficacy and safety of aliskiren are little known. Therefore, it does not seem that the scale of a special drug use-results survey proposed by the applicant is adequate. This survey should be positioned as exploratory where the aim is to select high priority items to be investigated later. (2) Since treatment discontinuation may be required due to unexpected or unnecessary increases in exposure, the information on the reasons for aliskiren discontinuation and treatments required should be collected. (3) In addition to investigating the safety and efficacy of aliskiren in the elderly aged ≥ 75 years, the safety and efficacy of aliskiren when co-administered with CYP3A4 inhibitors or P-glycoprotein inhibitors, and the relationship of the relation of administration to meals to the safety and efficacy of aliskiren as suggested by PMDA, the applicant should further collect the information on the relationship of gastrointestinal adverse drug reactions, mainly diarrhoea, to the local irritant effects of aliskiren as indicated in non-clinical studies.

Taking account of these comments etc., PMDA asked the applicant to explain whether the planned number of patients is large enough to investigate the safety and efficacy of aliskiren by patient background, e.g. decreased renal function, old age, and low body weight that may affect the efficacy and safety of aliskiren. PMDA also asked the applicant to consider specific parameters for data to be collected for conducting an appropriate investigation, including the information on concomitant medications and the reasons for aliskiren discontinuation.

The applicant submitted a special drug use-results survey plan and a case report form (draft) and responded as follows:
Based on the experience of post-marketing surveillance for a similar drug (ARB), the safety and efficacy of aliskiren according to patient background as indicated by PMDA can be investigated with the planned number of patients of 3000. If problems or questions are identified in the planned special drug use-results survey, the conduct of another special drug use-results survey or a post-marketing clinical study will be considered in order to detect or check their factors.

PMDA concluded that although the details of a case report form etc. need further improvement etc., the applicant's survey plan etc. is largely acceptable.

III. Overall Evaluation

As a result of the above review, PMDA considered that the product may be approved for the following indication and dosage and administration and concluded that the product application should be deliberated by the First Committee on New Drugs.

Since this product is classified as a drug with a new active ingredient, the appropriate re-examination period should be 8 years.

Neither the drug substance nor the drug product is classified as a poisonous drug or a powerful drug and the product is not classified as a biological product or a specified biological product.

[Indication]
Hypertension

[Dosage and administration]
Usually for adult dose, 150 mg of aliskiren is orally administered once daily. However, the dose may be escalated up to 300 mg if there is lack of efficacy.