Report on the Deliberation Results

February 26, 2019
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Rosuzet Combination Tablets LD
	Rosuzet Combination Tablets HD
Non-proprietary Name	Ezetimibe / Rosuvastatin Calcium (JAN*)
Applicant	MSD K.K.
Date of Application	May 22, 2018

Results of Deliberation

In its meeting held on February 21, 2019, 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 4 years. The drug products are not classified as a poisonous drug or a powerful drug.

Condition of Approval

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

**Japanese Accepted Name (modified INN)*

Review Report

February 8, 2019
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Rosuzet Combination Tablets LD Rosuzet Combination Tablets HD
Non-proprietary Name	Ezetimibe / Rosuvastatin Calcium
Applicant	MSD K.K.
Date of Application	May 22, 2018
Dosage Form/Strength	An uncoated tablet containing 10 mg ezetimibe and 2.5 mg rosuvastatin An uncoated tablet containing 10 mg ezetimibe and 5 mg rosuvastatin
Application Classification	Prescription drug, (2) New combination drug
Reviewing Office	Office of New Drug II

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

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

Indications
Hypercholesterolemia, familial hypercholesterolemia

Dosage and Administration
The usual adult dosage is one tablet (10 mg/2.5 mg or 10 mg/5 mg of ezetimibe/rosuvastatin) administered orally once daily after meal.

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

Attachment

Review Report (1)

December 4, 2018

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

Product Submitted for Approval

Brand Name	Rosuzet Combination Tablets LD
	Rosuzet Combination Tablets HD
Non-proprietary Name	Ezetimibe / Rosuvastatin Calcium
Applicant	MSD K.K.
Date of Application	May 22, 2018
Dosage Form/Strength	An uncoated tablet containing 10 mg ezetimibe and 2.5 mg rosuvastatin
	An uncoated tablet containing 10 mg ezetimibe and 5 mg rosuvastatin
Proposed Indications	Hypercholesterolemia, familial hypercholesterolemia
Proposed Dosage and Administration	The usual adult dosage is one tablet (10 mg/2.5 mg or 10 mg/5 mg of ezetimibe/rosuvastatin) administered orally once daily after meal.

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List of Abbreviations

See Appendix.

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

Rosuzet Combination Tablets (hereafter Rosuzet) are combination drugs containing ezetimibe (EZ) and rosuvastatin (RS) calcium as active ingredients. In Japan, EZ was approved for the indications of hypercholesterolemia, familial hypercholesterolemia, and homozygous sitosterolemia in 2007 and RS Calcium was approved for the indications of hypercholesterolemia and familial hypercholesterolemia in 2005.

EZ suppresses the intestinal absorption of food- and bile-derived cholesterol by inhibiting a cholesterol transporter, NPC1L1, expressing in small intestinal wall cells, and thereby reduces LDL-cholesterol (LDL-C); whereas RS suppresses the biosynthesis of cholesterol in the liver by inhibiting HMG-CoA reductase and thereby reduces LDL-C.

The applicant started to develop Rosuzet in Japan in 20[redacted], and submitted an application for its marketing approval on the basis of Japanese clinical study results. As of November 2018, Rosuzet is not approved in any countries or regions outside Japan.

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

2.1 Drug substance EZ

EZ is identical to the drug substance used for Zetia Tablets marketed by the applicant.

2.2 Drug substance RS Calcium

RS Calcium is registered in the Drug Master File (DMF Registration No. [redacted]) by [redacted]. The summary of data on RS Calcium submitted by [redacted] and the outline of review by PMDA, are presented in Supplement.

2.2.1 Characterization

Described in Supplement.

2.2.2 Manufacturing process

Described in Supplement.

2.2.3 Control of RS Calcium

The proposed specifications for RS Calcium include strength, description, identification (IR, HPLC, qualitative test), purity (related substances [HPLC], enantiomer [HPLC], residual solvents [GC]), water content, and assay (HPLC).

2.2.4 Stability of RS Calcium

Described in Supplement.

2.3 Drug products

2.3.1 Description and composition of drug products and formulation development

The drug products [redacted] containing 10 mg EZ and [redacted] containing 2.5 or 5 mg RS per tablet. The drug products contain excipients: lactose hydrate, crystalline cellulose, povidone, croscarmellose sodium, sodium lauryl sulfate, magnesium stearate, D-mannitol, low-substituted hydroxypropylcellulose, and hydroxypropylcellulose.

2.3.2 Manufacturing process

The drug products are manufactured through a process comprised of the following steps: acceptance testing, granulation, sizing, and lubricant mixing steps for EZ; acceptance testing, sieving, granulation, sizing, and lubricant mixing steps for RS Calcium; and tableting and packaging/labeling steps. The [redacted] and [redacted] steps for each drug substance have been defined as critical steps, and in-process control parameters and control values have been established for the critical steps and [redacted].

A quality control system based on the following have been established using the Quality by Design (QbD):

- Identification of critical quality attributes (CQAs)
- Identification of critical process parameters (CPP) through risk assessment and using experimental designs

Table 1. Outline of control methods of drug products

CQA	Control methods
[redacted]	Manufacturing process, specifications, and test methods
[redacted]	Specifications and test methods
[redacted] and [redacted]	Manufacturing process, specifications, and test methods
[redacted]	Manufacturing process, specifications, and test methods
[redacted]	Manufacturing process, specifications, and test methods
[redacted]	Manufacturing process, specifications, and test methods
[redacted]	Manufacturing process, specifications, and test methods

2.3.3 Control of drug products

The proposed specifications for the drug products consist of strength, description (visual), identification (HPLC, TLC), purity (related substances [HPLC]), uniformity of dosage units (content uniformity [HPLC]), dissolution (HPLC), and assay (HPLC).

2.3.4 Stability of drug products

Table 2 shows pivotal stability studies performed for the drug products. Photostability stress testing demonstrated that the drug products packaged in a blister pack were photostable.

Table 2. Pivotal stability studies

Test	Formulation	Primary batch	Temp.	Humidity	Package	Storage period
Long-term	Rosuzet Combination Tablets LD	3 pilot scale batches per formulation	25℃	60%RH	Blister pack[a] + aluminum bag	24 months
Accelerated	Rosuzet Combination Tablets HD		40℃	75%RH		6 months

[a] [redacted] red polyvinyl chloride + aluminum foil

On the basis of these results and the ICH Q1E guideline, a shelf life of 36 months has been proposed when the drug products are stored in a blister pack (made of [redacted] red polyvinyl chloride and aluminum foil) inside an aluminum bag at room temperature, protected from light. The long-term test will be continued for [redacted] months.

2.R Outline of the review conducted by PMDA

On the basis of the data submitted, the PMDA judged that the quality control of the drug substances and drug products was appropriate. The DMF data have been separately provided by the DMF registrants. The results of PMDA's review of the DMF data are presented in Supplement.

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

3.1 Primary pharmacodynamics

3.1.1 Blood cholesterol-lowering effects in hCETP-overexpressing mice (*J Lipid Res.* 2011;52:679-87 [reference data])

Female mice (16-20 weeks of age) engineered to be heterozygous for *Ldl* receptor deficiency ($Ldlr^{+/-}$) and the overexpression of *hCetp* driven by the *APOA1* promoter ($APOA1\text{-}hCetp^{+/-}$) were used for this study. These animals were orally given EZ 10 mg/kg alone, RS 20 mg/kg alone, EZ 10 mg/kg + RS 20 mg/kg, or vehicle once daily for 14 days while being fed with low-fat Western diet (8 animals per group). To investigate potential effects of the *PCSK9* expression induced by EZ, at Day 11 animals in the EZ, RS, and EZ + RS groups were given a single intravenous dose of (a) siRNAs designed against the mouse *Pcsk9* and formulated in lipid nanoparticles (LNP) (*Pcsk9* siRNA) or (b) LNP alone (control siRNA) (8-9 animals per group), and then their serum non-HDL-C was measured as an estimate of LDL-C (*J Lipid Res.* 2011;52:1084-97). Animals given control siRNA in addition to EZ, RS, or EZ + RS showed a 24%, 24%, and 65% decrease in serum non-HDL-C, respectively, compared with animals given control siRNA and vehicle. Animals given *Pcsk9* siRNA in

addition to vehicle, EZ, RS, or EZ + RS showed a 25%, 61%, 43%, and 82% decrease in serum non-HDL-C, respectively, compared with animals given control siRNA and vehicle.

3.R Outline of the review conducted by PMDA

The applicant's explanation about the safety pharmacology of EZ + RS Calcium combination therapy:

The safety pharmacology studies of EZ (new drug application data for Zetia Tablets) and safety pharmacology studies of RS Calcium (Interview Form for Crestor Tablets, ver. 20, October 2018) showed no noteworthy effects on the central nervous, cardiovascular, or respiratory system. These studies showed no overlapping of drug effects between animals given EZ and those given RS Calcium. In humans, EZ and RS showed no pharmacokinetic drug interaction, and exposures to EZ and RS Calcium in EZ + RS Calcium combination therapy were consistent to those in EZ and RS Calcium monotherapies (new drug application data for Zetia Tablets). On the basis of these results, the applicant judged that EZ + RS Calcium combination therapy is unlikely to cause additional safety concerns.

PMDA's view:

The primary pharmacodynamic data suggest that EZ + RS Calcium combination therapy has greater blood cholesterol-lowering effects than EZ or RS Calcium monotherapy. In view of the safety pharmacology of EZ and RS Calcium monotherapies and the applicant's explanation about pharmacokinetic drug interaction between EZ and RS Calcium in EZ + RS Calcium combination therapy, PMDA judges from the pharmacological viewpoint that EZ + RS Calcium combination therapy is unlikely to cause particular safety concerns.

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

No additional non-clinical pharmacokinetic data were submitted for the present application because pharmacokinetic interactions between EZ and RS Calcium in EZ + RS Calcium combination therapy had been evaluated during the regulatory review process for Zetia Tablets.

5. Toxicity and Outline of the Review Conducted by PMDA

Toxicity data on impurities were submitted.

5.1 Other toxicity studies

5.1.1 Toxicity of impurities

RS Impurity was detected at concentrations exceeding the safety threshold specified in "Impurities in New Drug Products" (PFSB/ELD Notification No. 0624001 dated June 24, 2003, by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare). In a repeated oral

dose toxicity study of RS Calcium (containing [redacted]% RS Impurity) in rats, the no observed adverse effect level (NOAEL) was determined to be 10 mg/kg/day. The dose of RS Impurity at the NOAEL is estimated to be [redacted] μg/kg/day, which is 183 times the maximum clinical dose.[1)] On the basis of these findings, the applicant considers that RS Impurity was shown to be safe in terms of general toxicity. No structural alerts for mutagenicity of RS Impurity were identified by an *in silico* analysis using QSAR software programs ([redacted] and [redacted]); the applicant therefore considers that RS Impurity was shown to be safe in terms of mutagenicity.

Table 3. Toxicity study of impurities

Test drug	Study system	Administration route	Administration period	Dose (mg/kg/day)	Main finding	NOAEL (mg/kg/day)	CTD
RS Calcium (containing [redacted]% RS Impurity)	M/F rats (Wistar)	Oral	1 month	0[a], 2, 6, 10	ALT increased[b] in rats given ≥2 mg/kg/day	10	4.2.3.7.6.1

[a] 0.5% (w/v) aqueous methylcellulose solution

[b] This finding was judged toxicologically insignificant by the applicant because it was a mild change with no relevant pathological findings.

5.R Outline of the review conducted by PMDA

PMDA's conclusion based on the submitted data and the following review:

The non-clinical toxicity evaluation identified no problems with the clinical use of Rosuzet.

5.R.1 Toxicity of EZ + RS Calcium combination therapy

The applicant did not conduct toxicity studies of EZ + RS Calcium combination therapy in the development of Rosuzet.

PMDA's view about this omission:

Potential toxicities of EZ and statins except RS Calcium were already evaluated in toxicity studies for the new drug application of Zetia Tablets. Further, no common target organs of toxicity were identified in toxicity studies of EZ and RS Calcium monotherapies (new drug application data for Zetia Tablets; *Toxicol Pathol.* 2004;32:26-41). Thus, EZ + RS Calcium combination therapy is unlikely to cause unknown toxicities or aggravate the known toxicities. It is therefore unnecessary to conduct additional non-clinical toxicity studies to evaluate potential toxicities of EZ + RS Calcium combination therapy.

1 The maximum amount of RS Impurity contained in Rosuzet (RS 5 mg/day equivalent) was calculated using its content specification of Rosuzet.

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

6.1 Summary of biopharmaceutic studies and associated analytical methods

The to-be-marketed drug products are combination tablet EZ 10 mg/RS 2.5 mg (Rosuzet LD, hereafter EZ 10 mg/RS 2.5 mg) and combination tablet EZ 10 mg/RS 5 mg (Rosuzet HD, hereafter EZ 10 mg/RS 5 mg). The bioequivalence (BE) between the 2 tablets have been demonstrated by dissolution studies conducted according to the Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms.

RS 2.5 mg tablet (Crestor Tablets 2.5 mg) [redacted] and EZ 10 mg tablet (Zetia Tablets), were used in a phase III study in patients with hypercholesterolemia (HC) (Study P832) and a long-term study in patients with HC or heterozygous familial hypercholesterolemia (HeFH) (Study P833). EZ 10 mg/RS 5 mg (Rosuzet HD, a to-be-marketed drug product) was used in a food-effect study (Study P836). Crestor Tablets 2.5 mg [redacted] used in Studies P832 and P833, were demonstrated to be bioequivalent to the original Crestor Tablets 2.5 mg by dissolution studies conducted according to the Guideline for Bioequivalence Studies for Formulation Changes of Oral Solid Dosage Forms.

Plasma concentrations of EZ and RS were determined by liquid chromatography-tandem mass spectrometry and their lower limits of quantification were 40 and 20 pg/mL, respectively.

6.1.1 Bioequivalence (a) (Study P835, CTD 5.3.1.1.1)

A two-by-two cross-over study with a 14-day recovery period was conducted in 118 Japanese healthy adults to determine the relative bioavailability (BA) of combination tablet EZ 10 mg/RS 5 mg (Rosuzet HD, hereafter EZ 10 mg/RS 5 mg) versus coadministration of EZ 10 mg tablet and RS 5 mg tablet (hereafter EZ 10 mg + RS 5 mg), administered orally as a single dose in the fasted state.

The geometric mean ratios (EZ 10 mg/RS 5 mg vs EZ 10 mg + RS 5 mg) of C_{max} and $AUC_{0\text{-}72h}$ (90% confidence interval [CI]) of EZ were 1.01 [0.95, 1.07] and 0.99 [0.96, 1.02], respectively, and those of RS were 0.99 [0.95, 1.03] and 1.00 [0.97, 1.03], respectively.

6.1.2 Bioequivalence (b) (Study P846, CTD 5.3.1.1.3)

A two-by-two cross-over study was conducted in Japanese healthy adults to investigate food effects on the pharmacokinetics (PK) of RS 5 mg tablet (Part 1, 14 subjects, a 7-day recovery period), and to determine the relative bioavailability of EZ 10 mg/RS 5 mg (Rosuzet HD) versus EZ 10 mg + RS 5 mg, administered in the fed state (Part 2, 122 subjects, a 14-day recovery period).

In Part 1, the geometric mean ratios (fed/fasted) of C_{max} and $AUC_{0\text{-}last}$ [90% CI] of RS were 0.33 [0.30, 0.37] and 0.44 [0.40, 0.49], respectively.

In Part 2, the geometric mean ratios (EZ 10 mg/RS 5 mg vs EZ 10 mg + RS 5 mg) of C_{max} and $AUC_{0\text{-}72h}$ [90% CI] of EZ were 0.99 [0.94, 1.05] and 0.98 [0.95, 1.01], respectively, and those of RS were 1.01 [0.97, 1.05] and 1.04 [1.01, 1.07], respectively.

6.1.3 Food effects (Study P836, CTD 5.3.1.1.2)

A two-by-two cross-over study with a 14-day recovery period was conducted to investigate food effects on the PK of EZ 10 mg/RS 5 mg administered orally as a single dose to 14 Japanese healthy adults in the fasted and fed state.

The geometric mean ratios (fed/fasted) of C_{max} and $AUC_{0\text{-}72h}$ [90% CI] of EZ were 0.84 [0.73, 0.96] and 0.85 [0.76, 0.95], respectively, and those of RS were 0.38 [0.31, 0.46] and 0.48 [0.41, 0.56], respectively.

6.2 Clinical pharmacology

No additional clinical pharmacology data were submitted for the present application. Potential pharmacokinetic interactions between EZ and RS Calcium in EZ + RS Calcium combination therapy had been evaluated during the regulatory review process for Zetia Tablets; the evaluation results showed that PK of EZ and RS Calcium in combination therapy did not greatly differ from those in individual monotherapies.

6.R Outline of the review conducted by PMDA

6.R.1 Bioequivalence

The applicant's explanation about the bioequivalence between (a) the to-be-marketed drug products (EZ 10 mg/RS 2.5 mg, EZ 10 mg/RS 5 mg) and (b) EZ 10 mg + RS 2.5 or 5 mg:

The bioequivalence studies (Studies P835 and P846) showed bioequivalence between EZ 10 mg/RS 5 mg and EZ 10 mg + RS 5 mg. No clinical studies have evaluated bioequivalence between (c) EZ 10 mg/RS 2.5 mg and (d) coadministration of EZ 10 mg + RS 2.5 mg (hereafter EZ 10 mg + RS 2.5 mg). Nevertheless, the therapies (c) (d) are considered to be bioequivalent, because EZ 10 mg/RS 2.5 mg was shown to be bioequivalent to EZ 10 mg/RS 5 mg [see Section "6.1 Summary of biopharmaceutic studies and associated analytical methods"], and because EZ 10 mg/RS 5 mg was shown to be bioequivalent to EZ 10 mg + RS 5 mg.

PMDA's view:

On the basis of the bioequivalence data submitted and the applicant's explanation, PMDA concludes that EZ 10 mg/RS 5 mg is bioequivalent to EZ 10 mg + RS 5 mg, and that EZ 10 mg/RS 2.5 mg is bioequivalent to EZ 10 mg + RS 2.5 mg.

6.R.2 Food effects

In Studies P836 and P846 (the food-effect studies), RS exposures (C_{max}, $AUC_{0\text{-last}}$) following administration of EZ 10 mg/RS 5 mg or RS 5 mg alone was lower in fed subjects than in fasted subjects. In the phase III studies (Studies P832 and P833), all study drugs were administered after meal. PMDA therefore asked the applicant to discuss whether alerts should be issued for HC patients who switch fasting intake of RS Calcium alone to fed intake of Rosuzet.

The applicant's explanation:

(a) Study P836 and Study P846 showed that exposures to RS was lower in fed administration (30 min after meal) than in fasted administration (subjects fasted from 10 h before to 4 h after administration). In clinical practice, however, very few patients are continuously receiving RS Calcium monotherapy in the same fasting condition as in Studies P836 and P846.

(b) According to the summary of new drug application data for Crestor Tablets, C_{max} and $AUC_{0\text{-}24h}$ of RS were 20% and 6% lower, respectively, in subjects receiving RS Calcium 10 mg immediately after meal (once daily for 14 days) than in those receiving the drug in the fasted state (3 h after evening meal).

The food effects on the PK of RS were milder in (b) than in (a), and this inconsistency is believed to be caused by differences in the fasting conditions between the studies in (a) and (b). In addition, the dosage regimen for RS Calcium monotherapy has no rules for food intake and patients are allowed to take the drug without considering the timing of food intake; this suggests that fluctuations in RS exposures due to food are considered to be clinically insignificant. The applicant therefore considers it unnecessary to add precautionary statements for patients who switch from fasting intake of RS Calcium monotherapy to fed intake of Rosuzet. However, the applicant will provide information in the packaging insert about the severity of food effects on the PK of RS after single oral administration of Rosuzet and RS Calcium monotherapy.

PMDA's view:

In Studies P836 and P846, RS exposure was lower after fed administration than after fasting administration for both Rosuzet HD (EZ 10 mg/RS 5 mg) and RS Calcium monotherapy. Therefore relevant data from Studies P836 and P846 should be provided in the packaging insert and other information materials. However, PMDA agreed to the applicant's opinion that patients in clinical practice are unlikely to continuously receive RS Calcium monotherapy in similar fasting conditions to those in Studies P836 and P846. In addition, considering the data suggesting that the severity of food effects on the PK of RS depends on the lag between food intake

and RS treatment, PMDA judges that food effects on the PK of RS may be clinically insignificant for HC patients who switch from fasting intake of RS Calcium monotherapy to fed intake of Rosuzet. After the launch of Crestor Tablets, there have been no reports suggesting unfavorable effects of the timing of food intake on the efficacy and safety of RS. Thus, PMDA concludes that no precautions are necessary for HC patients who switch from fasting intake of RS Calcium monotherapy to fed intake of Rosuzet.

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

The applicant submitted efficacy and safety evaluation data: 5 pivotal clinical studies listed in Table 4 [for PK studies, see Section "6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA"].

Table 4. List of pivotal clinical studies

Data category	Region	Study	Phase	Population	No. of subjects enrolled	Dosage regimen	Primary endpoints
Evaluation data	Japan	P836	I	Healthy adults	14	Single oral dose of EZ 10 mg/RS 5 mg in the fasted or fed state	PK, safety
		P835	I	Healthy adults	118	Single oral dose of EZ 10 mg/RS 5 mg or EZ 10 mg + RS 5 mg in the fasted state	PK, safety
		P846	I	Healthy adults	Part I: 14 Part II: 122	Part 1: Single oral dose of RS 5 mg in the fasted or fed state Part 2: Single oral dose of EZ 10 mg/RS 5 mg or EZ 10 mg + RS 5 mg in the fed state	PK, safety
		P832	III	HC patients	EZ 10 mg alone: 35 RS 2.5 mg alone: 72 RS 5 mg alone: 71 EZ 10 mg + RS 2.5 mg: 71 EZ 10 mg + RS 5 mg: 72	Once-daily oral administration of EZ 10 mg alone, RS 2.5 mg alone, RS 5 mg alone, EZ 10 mg + RS 2.5 mg, or EZ 10 mg + RS 5 mg in the fed state	Efficacy, safety
		P833	III	HC patients + HeFH patients	EZ 10 mg + RS 2.5 mg: 114 EZ 10 mg + RS 5 mg: 21	Once-daily oral administration of EZ 10 mg + RS 2.5 mg or EZ 10 mg + RS 5 mg in the fed state	Efficacy, safety

7.1 Phase I studies

7.1.1 Food effects (Study P836; CTD 5.3.1.1.2; study period, [redacted], 20[redacted])

A randomized, open-label, two-by-two cross-over study with a ≥14-day recovery period was conducted at a Japanese center to evaluate food effects on the PK of EZ 10 mg/RS 5 mg administered orally as a single dose to Japanese healthy adults in the fed or fasted state (target sample size, 14).

All 14 enrolled subjects received EZ 10 mg/RS 5 mg and were included in the safety analysis set (SAS). No subjects discontinued the study treatment.

The incidence of adverse events was 0% (0 of 14) of fasted subjects and 14.3% (2 of 14) of fed subjects (1 subject for diarrhea and eczema nummular; 1 subject for headache).

No deaths, serious adverse events, or adverse events leading to discontinuation of study treatment were observed.

7.1.2 Bioequivalence (a) (Study P835; CTD 5.3.1.1.1; study period, [redacted], 20[redacted])

A randomized, open-label, two-by-two cross-over study with a 14-day recovery period was conducted at a Japanese center to determine the relative bioavailability of EZ 10 mg/RS 5 mg versus EZ 10 mg + RS 5 mg (target sample size, 118).

EZ 10 mg/RS 5 mg or EZ 10 mg + RS 5 mg was administered orally as a single dose to Japanese healthy adults in the fasted state.

All 118 enrolled subjects received the study treatment and were included in the SAS. Two subjects discontinued study treatment because of an adverse event (in one subject) and no study visit (in the other subject).

The incidence of adverse events was 0.9% (1 of 117) of subjects receiving EZ 10 mg/RS 5 mg (influenza), and 1.7% (2 of 117) of subjects receiving EZ 10 mg + RS 5 mg (1 subject each for influenza and blood creatine phosphokinase increased).

No deaths or serious adverse events were observed. One subject experienced an adverse event leading to discontinuation of study treatment (influenza); this event was unrelated to study treatment.

7.1.3 Bioequivalence (b) (Study P846; CTD 5.3.1.1.3; study period, [redacted], 20[redacted])

A randomized, open-label, two-by-two cross-over study was conducted at a Japanese center to investigate food effects on the PK of RS 5 mg (Part 1: 7-day recovery period; target sample size, 14), and to determine the relative bioavailability of EZ 10 mg/RS 5 mg versus EZ 10 mg + RS 5 mg, both administered after meal (Part 2: 14-day recovery period; target sample size, 120).

In Part 1, Japanese healthy adults received a single oral dose of RS 5 mg alone in the fed or fasted state. In Part 2, Japanese healthy adults received a single oral dose of EZ 10 mg/RS 5 mg or EZ 10 mg + RS 5 mg after meal.

In Part 1, all 14 enrolled subjects received the study treatment and were included in the SAS. In Part 2, all 122 enrolled subjects received the study treatment and were included in the SAS. In this study, 3 subjects discontinued study treatment at Part 2 because of adverse events in 2 subjects and no study visit in 1 subject.

In Part 1, no adverse events occurred.

In Part 2, the incidence of adverse events was 2.5% (3 of 120) of subjects receiving EZ 10 mg/RS 5 mg (1 subject each for arthropod sting, hematuria, tooth repair), and 0.8% (1 of 120) of subjects receiving EZ 10 mg + RS 5 mg (nasopharyngitis).

No deaths or serious adverse events were observed in either Part 1 or 2. Two subjects experienced adverse events leading to discontinuation of the study treatment (1 subject each for nasopharyngitis and hematuria); these events were unrelated to study treatment.

7.2 Phase III studies

7.2.1 Phase III study in HC patients (Study P832; CTD 5.3.5.1.1; study period, June 2016 to January 2017)

A randomized, double-blind, parallel-group study was conducted at 20 Japanese centers to compare the efficacy and safety of EZ 10 mg + RS 2.5 mg or EZ 10 mg + RS 5 mg with those of EZ 10 mg, RS 2.5 mg, or RS 5 mg monotherapy in HC patients (target sample size: 34 patients in the EZ 10 mg group and 68 patients each in the other groups; 306 patients in total). Patients were stratified by the Risk Control Classification of Japan Atherosclerosis Society (JAS) Guideline 2012 (primary prevention category I, II, and III), and were assigned to one of the following groups at a ratio of 1:2:2:2:2: EZ 10 mg, RS 2.5 mg, RS 5 mg, EZ 10 mg + RS 2.5 mg, or EZ 10 mg + RS 5 mg, respectively.

After a screening period of up to 6 weeks, patients received placebo orally once daily in the fed state during a 2-week single-blind observation period. Then they received EZ 10 mg, RS 2.5 mg, RS 5 mg, EZ 10 mg + RS 2.5 mg, or EZ 10 mg + RS 5 mg orally once daily in the fed state during a 12-week double-blind treatment period. Patients were not allowed to use antihyperlipidemic drugs other than the study drugs from the start of the screening period until the end of the double-blind treatment period.

The study included HC patients aged ≥20 and ≤80 years at the time of consent acquisition who met any of the criteria for LDL-C (Friedewald formula):

- Primary prevention category I[2)]: LDL-C, ≥160 mg/dL, <220 mg/dL
- Primary prevention category II[2)]: LDL-C, ≥140 mg/dL, <190 mg/dL
- Primary prevention category III[2)]: LDL-C, ≥120 mg/dL, <160 mg/dL

[2)] Risk control classification based on JAS Guideline 2012

The 321 randomized patients received the study drugs (EZ 10 mg, 35 patients; RS 2.5 mg, 72 patients; RS 5 mg, 71 patients; EZ 10 mg + RS 2.5 mg, 71 patients; EZ 10 mg + RS 5 mg, 72 patients; hereinafter in the same order). All of the 321 patients were included in the SAS and full analysis set (FAS). FAS was used for efficacy analysis. During the double-blind treatment period, 7 patients (0 patients, 1 patient, 0 patients, 4 patients, 2 patients) discontinued the study treatment mainly because of adverse events (0 subjects, 0 subjects, 0 subjects, 2 subjects, 2 subjects).

Table 5 shows changes in LDL-C[3)] from baseline (i.e., the start of double-blind treatment period) to Week 12 of the double-blind treatment period; this is the primary efficacy endpoint. The changes significantly differed between the EZ 10 mg + RS 2.5 mg and EZ 10 mg groups, between the EZ 10 mg + RS 2.5 mg and RS 2.5 mg groups, between the EZ 10 mg + RS 5 mg and EZ 10 mg groups, and between the EZ 10 mg + RS 5 mg and RS 5 mg groups ($p < 0.001$ for each). This robust regression analysis[4)] used treatment group and risk control classification (primary prevention category I, II, and III) as factors and baseline LDL-C as covariate, and missing values were imputed with multiple imputation, and multiplicity was adjusted with the Hochberg method.[5)]

3) The Friedewald formula was used for TG ≤400 mg/dL and the direct method for TG >400 mg/dL.

4) Because the normality of the residuals in a cLDA (constrained longitudinal data analysis) model was statistically significant ($p<0.001$, Shapiro-Wilk test), the robust regression method was used in primary analysis as specified in the study protocol.

5) Each of the 2 comparison pairs (EZ 10 mg + RS 2.5 mg versus each monotherapy; EZ 10 mg + RS 5 mg versus each monotherapy) was treated as a family of hypotheses. For each family, multiplicity was adjusted by using Hochberg's method. Significant differences must be demonstrated in comparison of each of the 2 pairs.

Table 5. Changes in LDL-C from baseline to Week 12 of double-blind treatment period (FAS)

	EZ 10 mg	RS 2.5 mg	RS 5 mg	EZ 10 mg + RS 2.5 mg	EZ 10 mg + RS 5 mg
Baseline (mg/dL)					
n	35	72	71	71	72
Mean ± standard deviation	162.6 ± 23.3	164.5 ± 22.4	163.3 ± 23.0	160.6 ± 22.7	166.6 ± 22.3
At Week 12 of double-blind treatment period (mg/dL)					
n	35	72	71	71	72
Mean ±standard deviation	134.7 ± 21.2	101.5 ± 22.6	88.2 ± 19.2	76.9 ± 21.1	69.7 ± 25.9
Change from baseline (mg/dL)					
n	35	70	70	66	67
Mean ±standard deviation	−27.9 ± 24.9	−62.5 ± 25.3	−74.7 ± 26.2	−83.7 ± 29.9	−97.1±27.9
Change from baseline (%)					
n	35	72	71	71	72
Mean ±standard deviation	−16.1 ± 14.7	−37.6 ± 14.1	−45.1 ± 13.1	−51.4 ± 14.8	−58.2 ± 14.2
M-estimator[a] ± standard error[b]	−18.7 ± 1.6	−39.8 ± 1.2	−47.2 ± 1.1	−54.6 ± 1.2	−60.5 ± 1.2
Difference from EZ 10 mg + RS 2.5 mg[b]					
M-estimator	−35.9	−14.8			
[95% CI]	[−39.9, −32.0]	[−18.0, −11.6]	–	–	–
P value	<0.001	<0.001			
Difference from EZ 10 mg + RS 5 mg[b]					
M-estimator	−41.8		−13.3		
[95% CI]	[−45.8, −37.9]	–	[−16.6, −10.1]	–	–
P value	<0.001		<0.001		

[a] *Ann Stat.* 1973;1:799-821

[b] Robust regression analysis using treatment group and risk control class (primary prevention category I, II, or III) as fixed effects, and baseline LDL-C as covariant

Main adverse events and their incidences are shown in Table 6.

Table 6. Incidences of adverse events (safety analysis set)

	EZ 10 mg (n = 35)	RS 2.5 mg (n = 72)	RS 5 mg (n = 71)	EZ 10 mg + RS 2.5 mg (n = 71)	EZ 10 mg + RS 5 mg (n = 72)
Any adverse event	31.4 (11)	34.7 (25)	42.3 (30)	40.8 (29)	37.5 (27)
Nasopharyngitis	17.1 (6)	11.1 (8)	15.5 (11)	8.5 (6)	9.7 (7)

% (number of patients)

No deaths occurred. One patient in the RS 5 mg group experienced a serious adverse event (bacterial prostatitis); this event was unrelated to study treatment.

Adverse events leading to discontinuation of study treatment occurred in 2 patients of the EZ 10 mg + RS 2.5 mg group (ALT increased and γ-GTP increased in one patient; rash in the other patient) and 1 patient of the EZ 10 mg + RS 5 mg group (back pain).

7.2.2 Long-term study in HC patients (Study P833, CTD 5.3.5.2.1; study period, May 2016 to December 2017)

An open-label study was conducted at 19 Japanese centers to investigate the efficacy and safety of long-term treatment with EZ 10 mg + RS 2.5 mg or EZ10 mg + RS 5 mg in HC patients who had an inadequate response to monotherapy with EZ 10 mg, RS 2.5 mg, or RS 5 mg (target sample size: 134 patients in total).

If patients had been receiving monotherapy with EZ 10 mg, RS 2.5 mg, or RS 5 mg for at least 4 weeks before the start of the screening period, they continued to receive their respective treatment during the 4-week screening period. During the 52-week treatment period, patients received oral administration of EZ 10 mg + RS 2.5 mg (if they had received EZ 10 mg or RS 2.5 mg during the screening period) or EZ 10 mg + RS 5 mg (if they had received RS 5 mg during the screening period) once daily after meal. In principle, dose changes of the study drugs were not allowed during the 52-week treatment period. However, if LDL-C did not reach the target lipid value at Week ≥12 of treatment, patients receiving EZ 10 mg + RS 2.5 mg were allowed to increase their dose to EZ 10 mg + RS 5 mg from the next scheduled visit (Week 20, 24, 32, or 40 of treatment) if the dose increase was considered safe by the investigator. In principle, patients were not allowed to use antihyperlipidemic drugs other than the study drugs from the start of screening until the end of study. However, if LDL-C did not reach the target lipid value after ≥12 weeks of treatment with EZ 10 mg + RS 5 mg, patients were allowed to use additional antihyperlipidemic drugs other than the study drugs (except statins other than RS) from the next scheduled visit at investigator's discretion.

The study included HC patients aged ≥20 and ≤80 years at consent provision who had been receiving monotherapy with EZ 10 mg, RS 2.5 mg, or RS 5 mg without changing the dosage for at least 4 weeks at the start of screening, and met any of the following LDL-C (Friedewald formula) criteria:

- Primary prevention category I[2)]: LDL-C ≥160 mg/dL
- Primary prevention category II[2)]: LDL-C ≥140 mg/dL
- Primary prevention category III[2)]: LDL-C ≥120 mg/dL
- Secondary prevention with a history of coronary heart disease[2)] or HeFH[6)]: LDL-C ≥100 mg/dL

In this study, 135 patients received study treatment (EZ 10 mg + RS 2.5 mg, 114 patients; EZ 10 mg + RS 5 mg, 21 patients; hereinafter in the same order), and all of the patients were included in the SAS and FAS. FAS was used for efficacy analysis. During the treatment period, 7 patients (5 patients, 2 patients) discontinued study treatment mainly because of severe deviations from the protocol (2 patients, 1 patient).

[6)] Patients who was diagnosed as having HeFH on the basis of genetic test or those who met at least two of the criteria based on the JAS Guideline 2012: (1) an untreated LDL-C level of ≥180 mg/dL; (2) tendon xanthoma (tendon xanthoma on the backs of the hands, elbows, knees, etc. or Achilles tendon hypertrophy) or xanthoma tuberosum; (3) family history of FH or premature coronary arterial disease (within the second degree of consanguinity).

Changes (%) from baseline (Week 0 of treatment) in LDL-C[3)], an efficacy endpoint, are shown in Table 7.

Table 7. Changes from baseline in LDL-C (FAS)

		EZ 10 mg + RS 2.5 mg	EZ 10 mg + RS 5 mg
Baseline (mg/dL)		142.5 ± 33.5 (114)	146.6 ± 43.0 (21)
Changes (%)	Week 12	−35.7 ± 15.0 (111)	−25.1 ± 9.3 (20)
	Week 24	−33.5 ± 17.2 (111)	−25.3 ± 12.5 (19)
	Week 32	−34.2 ± 16.7 (111)	−26.4 ± 10.9 (18)
	Week 40	−33.9 ± 15.0 (111)	−28.8 ± 14.6 (17)
	Week 52	−33.8 ± 15.9 (108)	−23.9 ± 10.2 (17)

Mean ± standard deviation (number of patients)

Main adverse events and their incidences are shown in Table 8.

Table 8. Incidences of adverse events (SAS)

	EZ 10 mg + RS 2.5 mg (n = 114)	EZ 10 mg + RS 5 mg (n = 21)
Any adverse event	72.8 (83)	76.2 (16)
Nasopharyngitis	36.0 (41)	38.1 (8)
Back pain	7.9 (9)	4.8 (1)
Gastroenteritis	7.0 (8)	4.8 (1)
Influenza	4.4 (5)	4.8 (1)
Gingivitis	3.5 (4)	4.8 (1)
Blood CK increased	4.4 (5)	0 (0)
Liver function test abnormal	2.6 (3)	9.5 (2)
Type 2 diabetes mellitus	2.6 (3)	9.5 (2)
Headache	4.4 (5)	0 (0)
Contusion	1.8 (2)	9.5 (2)

% (number of patients)

No deaths occurred. Serious adverse events occurred in 2 patients of the EZ 10 mg + RS 2.5 mg group (1 patient each for intestinal adenocarcinoma and anxiety disorder) and 1 patient of the EZ 10 mg + RS 5 mg group (intervertebral disc protrusion); all of the events were unrelated to study treatment.

An adverse event leading to discontinuation of study treatment occurred in 1 patient of the EZ 10 mg + RS 2.5 mg group (blood CK increased); a causal relationship between the event and study treatment was not ruled out.

7.R Outline of the review conducted by PMDA

7.R.1 Clinical Significance of combining EZ and RS Calcium in a tablet

The applicant's explanation about combining EZ and RS Calcium in a tablet:

EZ + RS Calcium combination therapy can decrease blood LDL-C through two different mechanisms: the inhibitory effect of EZ on cholesterol uptake in the small intestine and the inhibitory effect of RS on cholesterol synthesis in the liver. EZ + RS Calcium combination therapy has been shown to more reduce LDL-C than RS

Calcium monotherapy by Study P832 and other clinical studies (e.g., *Am J Cardiol*. 2011;108:523-30; *Cardiovasc Ther*. 2016;34:371-82)

The JAS Guideline 2012, which was effective in Japan at the start of the Phase III study in 20[redacted], recommends statins for hyper LDL cholesterolemia as the first line therapy and statin + EZ combination therapy for patients with inadequate response to statin monotherapy; this therapeutic policy is unchanged in the JAS Guideline 2017. In addition, the JAS Guideline 2017 states that EZ is one of the drugs with proven anti-arteriosclerosis effects when used in combination with statins, and that statin + EZ combination therapy prevents the onset of arteriosclerosis in patients with acute coronary syndrome (ACS) (evidence level, 1+[7]; recommendation level, B[8]). The 2016 ESC/EAS Guideline (*Atherosclerosis.* 2016;253:281-344) in Europe, 2013 ACC/AHA Guideline (*Am Coll Cardiol.* 2014;63:2889-934) in the US, and 2016 ACC Expert consensus decision (*J Am Coll Cardiol.* 2016;68:92-125) also recommend healthcare professionals to consider using a statin as the first-line treatment and then adding EZ for patients with inadequate response to statins in the treatment of atherosclerotic diseases. Thus, EZ + RS Calcium combination therapy is expected to decrease LDL-C more and contribute to reducing the incidences of cardiovascular events.

A survey was conducted to investigate clinical experience with EZ + RS Calcium combination therapy based on [redacted] database (survey period, [redacted], 20[redacted]). The survey identified patients receiving antihyperlipidemic drugs (estimated number of patients, [redacted]), including those receiving EZ + 1 or more antihyperlipidemic drugs (estimated number of patients, [redacted]). Among patients receiving EZ + 1 or more antihyperlipidemic drugs, 30.7% were using EZ + RS Calcium. According to another survey conducted in 20[redacted] based on the same database (survey period, [redacted], 20[redacted]), EZ + RS Calcium were used by 44.5% and 54.5% of HC and FH patients, respectively, who were treated with EZ + statin combination therapy.

As described above, combining EZ and RS Calcium in a tablet is scientifically appropriate, considering the treatment guidelines for arteriosclerosis in and outside Japan, the action mechanism of both drugs, and a body of evidence of improved outcome after the combination treatment. The combination tablet of EZ / RS Calcium is clinically meaningful, considering that these drugs are commonly used in combination in Japan.

PMDA's view:

EZ + statin is one of the combination therapies recommended by guidelines in and outside Japan, and combining these drugs with different mechanisms of action is a reasonable way to achieve effective lipid control. The clinical experience with EZ + RS Calcium in Japan (i.e., the combination therapy has already been

[7] Randomized controlled trials and meta-analysis and systematic reviews of the trials
[8] Suggestion

used in Japanese clinical practice) and the submitted clinical study data on Rosuzet, indicate that coadministration of the 2 ingredients has clinically meaningful efficacy and therefore combining them in a single tablet is scientifically reasonable. It is thus meaningful to provide patients with the combination tablet as an option of EZ + RS Calcium combination therapy.

7.R.2 Dosage and administration

7.R.2.1 Selection of fixed combination doses

The applicant's explanation about appropriateness of the proposed fixed combination doses:

Because EZ 10 mg once daily is approved in Japan, the dose of EZ in Rosuzet was set at 10 mg. In Japan, the usual initial and maximum doses of RS Calcium are RS 2.5 and 10 mg once daily, respectively, and patients receiving RS 10 mg are allowed to increase the dose to ≤20 mg if they have severe conditions (e.g., FH) and have failed to achieve a sufficient decrease in LDL-C after treatment with RS 10 mg. On the basis of the approved dosage of RS and the clinical experience with RS described below, the doses of RS in Rosuzet were set at 2.5 and 5 mg.

- In post-marketing surveillance of EZ (a long-term specified use-results survey), the mean daily doses of RS received by 168 users of EZ + RS combination therapy were as follows: 2.5 mg in 57.7% of users, 5 mg in 30.4% of users, 10 mg in 6.0% of users, and 20 mg in 2.4% of users.

- A survey was conducted to investigate clinical experience with EZ + RS Calcium combination therapy based on [redacted] database (survey period, [redacted], 20[redacted]) during the planning of Studies P832 and P833. According to the survey, 54.5% and 35.3% of EZ + RS Calcium users were receiving RS 2.5 and 5 mg/day, respectively; this means that approximately 90% of the users received either RS 2.5 or 5 mg/day.

Efficacy results:

Study P832 demonstrated significant differences in LDL-C change from baseline between HC patients receiving EZ + RS Calcium and those receiving either EZ or RS monotherapy (i.e., EZ 10 mg + RS 2.5 mg vs EZ 10 mg or RS 2.5 mg alone; EZ 10 mg + RS 5 mg vs EZ 10 mg or RS 5 mg alone). Further, HC patients receiving EZ 10 mg + RS 5 mg had a greater decrease in LDL-C than those receiving EZ 10 mg + RS 2.5 mg. In the long-term study (Study P833), the LDL-C-lowering effect of EZ + RS Calcium combination therapy continued without diminishing, and the effect was also observed in HeFH patients.

Safety results:

In Study P832, the incidence of adverse events in EZ + RS Calcium combination therapy (EZ 10 mg + RS 2.5 mg, EZ 10 mg + RS 5 mg) did not greatly differ from those in monotherapy with EZ 10 mg, RS 2.5 mg, or RS

5 mg; the individual adverse events in the combination therapy were known ones of each monotherapy [See Section "7.R.4 Safety"]. In Study P833, the long-term treatment with EZ + RS Calcium (EZ 10 mg + RS 2.5 mg, EZ 10 mg + RS 5 mg) did not increase the incidence of adverse events.

Based on these findings, the applicant considers the proposed doses of Rosuzet, EZ 10 mg/RS 2.5 mg and EZ 10 mg/RS 5 mg, are appropriate.

PMDA's view:

The applicant evaluated EZ 10 mg +RS 2.5 mg and EZ 10 mg + RS 5 mg on the basis of the preceding clinical study results and clinical experience in Japan; this was appropriate. In Study P832, EZ + RS Calcium combination therapy showed a significantly greater LDL-C-lowering effect than RS and EZ monotherapies (i.e., EZ 10 mg + RS 2.5 mg vs EZ 10 mg or RS 2.5 mg alone; EZ 10 mg + RS 5 mg vs EZ 10 mg or RS 5 mg alone), and EZ 10 mg/RS 5 mg (Rosuzet HD) showed a greater LDL-C-lowering effect than EZ 10 mg/RS 2.5 mg (Rosuzet LD). The submitted data demonstrated that there was no tendency toward decreased efficacy in long-term use of Rosuzet, and that the safety profile of Rosuzet is acceptable when weighed against its efficacy. In addition to these clinical study results, the dose combinations of EZ 10 mg +RS 2.5 mg and EZ 10 mg + RS 5 mg are commonly prescribed for patients who receive EZ + RS combination therapy in clinical settings. Thus the proposed doses of EZ 10 mg/RS 2.5 mg and EZ 10 mg/RS 5 mg are appropriate.

7.R.2.2 Target population and dosage and administration

The applicant's explanation about the proposed precautionary statements about target population and dosage and administration for Rosuzet:

Rosuzet is expected to be used in patients who switch from coadministration of EZ + RS Calcium, or in patients who have inadequate response to monotherapy with EZ or RS Calcium. The following statements will therefore be included in the Precautions for Dosage and Administration section in the packaging insert:

Precautions for Dosage and Administration (excerpts regarding prior treatments from the application documents)

- In principle, treatment with Rosuzet LD (ezetimibe 10 mg/rosuvastatin 2.5 mg) should be considered only for patients who are receiving ezetimibe 10 mg + rosuvastatin 2.5 mg combination therapy or those who inadequately respond to monotherapy with ezetimibe 10 mg or rosuvastatin 2.5 mg.
- In principle, treatment with Rosuzet HD (ezetimibe 10 mg/rosuvastatin 5 mg) should be considered only for patients who are receiving ezetimibe 10 mg + rosuvastatin 5 mg combination therapy or those who inadequately respond to rosuvastatin 5 mg monotherapy or ezetimibe 10 mg/rosuvastatin 2.5 mg.

PMDA's view about the target population and precautions for dosage and administration:

Rosuzet is a combination tablet containing EZ 10 mg/RS 2.5 mg or EZ 10 mg/RS 5 mg, and therefore should be used as an alternative to EZ 10 mg + RS 2.5 or 5 mg combination therapy in patients who are achieving stable LDL-C levels with the combination therapy. Patients with an inadequate response to RS 2.5 or 5 mg monotherapy have the option of increasing the RS dose, but they should also be allowed to switch to Rosuzet if their condition permits, because the addition of EZ 10 mg to RS was shown to further decrease LDL-C in clinical studies. On the basis of the results of Studies P832 and P833 [see Sections "7.2.1 Phase III study in HC patients" and "7.2.2 Long-term study in HC patients"], PMDA considers that patients with an inadequate response to EZ 10 mg + RS 2.5 mg combination therapy or Rosuzet LD should be allowed to switch to Rosuzet HD. However, the switch from EZ 10 mg monotherapy to Rosuzet should not be recommended to patients who have an inadequate response to EZ 10 mg alone, for the following reason:

> Statins have established their importance in preventing atherosclerotic diseases and JAS Guideline 2017 recommends statins as the first-line treatment of HC, but still there are patients being treated with EZ monotherapy. This suggests that many patients on EZ monotherapy cannot use concomitant RS Calcium because of intolerability to statins and other reasons.

For these reasons, PMDA requested that the applicant appropriately amend the wording of Precautions for Dosage and Administration.

The applicant agreed to delete the statement that permits switching EZ monotherapy to Rosuzet in the Precautions for Dosage and Administration section. PMDA accepted it.

7.R.3 Indications

The applicant's explanation about the indication:

In Study P832, EZ 10 mg + RS 2.5 or 5 mg combination therapy showed a significantly greater LDL-C lowering effect than corresponding EZ or RS monotherapy in HC patients with no additional safety risks associated with the combination therapy, although FH patients were not included in the study.

In Study P833, 36 patients (26.7% of all enrolled patients) had HeFH. In 31 of the 36 patients, LDL-C (mean ± standard deviation) was 140.6 ± 41.4 mg/dL at baseline and 100.7 ± 24.6 mg/dL at Week 52, and the change from baseline was −39.9 ± 30.8 mg/dL (−26.1 ± 15.1%). (The remaining 5 patients were excluded because they received additional other antihyperlipidemic drugs.) These results show that Rosuzet has an LDL-C lowering effect also in HeFH patients. EZ + RS Calcium combination therapy was well tolerated also in HeFH patients.

No clinical studies have evaluated the doses of EZ and RS calcium contained in Rosuzet (i.e., EZ 10 mg + RS 2.5 mg or EZ 10 mg + RS 5 mg) in patients with homozygous familial hypercholesterolemia (HoFH). However, both EZ and RS Calcium monotherapies have been approved for treatment of HoFH, and a phase III study of lomitapide (a drug already approved for treatment of HoFH) reported 3 Japanese patients who were treated with EZ + RS Calcium combination therapy (*J Atheroscler Thromb.* 2017;24:402-11). Therefore providing Rosuzet as a therapeutic option for HoFH patients is meaningful.

Based on the above discussion, the applicant proposed the indications of "hypercholesterolemia, familial hypercholesterolemia" for Rosuzet. These indications are the same as those of EZ and RS Calcium monotherapies.

PMDA's view:

The proposed indication of hypercholesterolemia (non-familial) is appropriate because Study P832 has demonstrated the efficacy and safety of EZ 10 mg + RS 2.5 or 5 mg combination therapy in non-familial HC patients. The other indication, familial hypercholesterolemia, is also appropriate because (1) both EZ and RS Calcium monotherapies have been used in FH patients in clinical practice; and (2) Study P833 demonstrated the clinical efficacy and acceptable safety of EZ 10 mg + RS 2.5 or 5 mg combination therapy in patients with HeFH. Considering these findings, PMDA has concluded that the proposed indications of "hypercholesterolemia, familial hypercholesterolemia" are acceptable.

7.R.4 Safety

7.R.4.1 Expected adverse events of Rosuzet based on adverse events of each active ingredient

The applicant's explanation about expected adverse events of Rosuzet based on adverse events of each active ingredient:

On the basis of adverse events characteristic of EZ and RS Calcium monotherapies, the applicant evaluated the incidences of the following adverse events: muscle-related events, liver-related events, hypersensitivity, interstitial lung disease, platelet count decreased, peripheral neuropathy, and erythema multiforme. Table 9 shows the incidences of muscle-related events,[9)] liver-related events,[10)] hypersensitivity-related events,[11)] and peripheral neuropathy-related events[12)] in clinical studies (Studies P832 and P833). There were no interstitial

[9)] Events coded as MedDRA SMQ "rhabdomyolysis/myopathy" and the preferred term (PT), "immune-mediated adverse reaction"

[10)] Events coded as MedDRA SMQ, "cholestasis and jaundice of hepatic origin," "hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions," "hepatitis, non-infectious," "liver related investigations, signs and symptoms," or "liver-related coagulation and bleeding disturbances"

[11)] Events coded as MedDRA SMQ "hypersensitivity"

[12)] Events coded as MedDRA SMQ "neuropathy peripheral"

lung disease-related events,[13] decreased platelet count-related events,[14] or erythema multiforme-related events.[15]

Table 9. Incidences of adverse events expected from EZ and RS Calcium (SAS)

	Study P832					Study P833	
	EZ 10 mg (n = 35)	RS 2.5 mg (n = 72)	RS 5 mg (n = 71)	EZ 10 mg + RS 2.5 mg (n = 71)	EZ 10 mg + RS 5 mg (n = 72)	EZ 10 mg + RS 2.5 mg (n = 114)	EZ 10 mg + RS 5mg (n = 21)
Muscle-related events							
Serum CK increased	2.9 (1)	1.4 (1)	1.4 (1)	0.0 (0)	0.0 (0)	4.4 (5)	0.0 (0)
Musculoskeletal pain	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	2.8 (2)	1.8 (2)	4.8 (1)
Myalgia	0.0 (0)	1.4 (1)	1.4 (1)	0.0 (0)	1.4 (1)	0.9 (1)	0.0 (0)
Renal dysfunction	0.0 (0)	0.0 (0)	1.4 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Liver-related events							
Hepatic steatosis	0.0 (0)	1.4 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.9 (1)	0.0 (0)
ALT increased	0.0 (0)	2.8 (2)	1.4 (1)	4.2 (3)	4.2 (3)	1.8 (2)	0.0 (0)
AST increased	0.0 (0)	0.0 (0)	0.0 (0)	2.8 (2)	0.0 (0)	0.9 (1)	0.0 (0)
γ-GTP increased	0.0 (0)	0.0 (0)	0.0 (0)	1.4 (1)	0.0 (0)	1.8 (2)	4.8 (1)
Liver function test abnormal	0.0 (0)	0.0 (0)	1.4 (1)	1.4 (1)	0.0 (0)	2.6 (3)	9.5 (2)
Liver disorder	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.9 (1)	0.0 (0)
Liver function test increased	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	1.8 (2)	0.0 (0)
Hypersensitivity-related events							
Stomatitis	0.0 (0)	1.4 (1)	1.4 (1)	1.4 (1)	0.0 (0)	0.9 (1)	0.0 (0)
Asthma	0.0 (0)	0.0 (0)	0.0 (0)	1.4 (1)	0.0 (0)	0.9 (1)	0.0 (0)
Dermatitis	0.0 (0)	1.4 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Dermatitis contact	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	1.4 (1)	0.9 (1)	4.8 (1)
Eczema	0.0 (0)	0.0 (0)	1.4 (1)	0.0 (0)	0.0 (0)	0.9 (1)	4.8 (1)
Erythema	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	1.4 (1)	0.0 (0)	0.0 (0)
Pruritus	0.0 (0)	0.0 (0)	1.4 (1)	0.0 (0)	0.0 (0)	0.9 (1)	0.0 (0)
Rash	0.0 (0)	0.0 (0)	0.0 (0)	1.4 (1)	0.0 (0)	1.8 (2)	0.0 (0)
Urticaria	0.0 (0)	0.0 (0)	1.4 (1)	1.4 (1)	0.0 (0)	0.0 (0)	4.8 (1)
Conjunctivitis allergic	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.9 (1)	0.0 (0)
Allergy to chemicals	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	4.8 (1)
Seasonal allergy	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.9 (1)	0.0 (0)
Conjunctivitis	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	1.8 (2)	0.0 (0)
Dermatitis allergic	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.9 (1)	0.0 (0)
Peripheral neuropathy-related events							
Hypoesthesia	0.0 (0)	0.0 (0)	0.0 (0)	1.4 (1)	1.4 (1)	1.8 (2)	0.0 (0)
Neuralgia	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.9 (1)	0.0 (0)

% (number of patients)

EZ + RS Calcium combination therapy did not increase the incidence or severity of muscle-related events or hypersensitivity-related events compared with either EZ or RS Calcium monotherapy, with no trend toward greatly increased incidence or severity in long-term combination therapy.

[13] Events coded as MedDRA SMQ “interstitial lung disease”
[14] Events coded as MedDRA SMQ “hematopoietic leucopenia”
[15] Events coded as MedDRA SMQ (narrow) “severe cutaneous adverse reactions”

EZ + RS Calcium combination therapy tended to slightly increase the incidence of liver-related events compared with EZ and RS Calcium monotherapies; however, all of the events were mild in severity. There were no trends toward greatly increased incidence or severity in long-term combination therapy.

Peripheral neuropathy-related events were observed only in EZ + RS Calcium combination therapy; however, their incidence was low and they were mild in severity. In long-term combination therapy, there were no trends toward increased incidence of the events, and the events observed were mild in severity.

These results show that EZ + RS Calcium combination therapy would not pose additional safety issues regarding adverse events expected from EZ and RS Calcium monotherapies. Therefore the packaging insert for Rosuzet will include only the precautionary statements provided in the package inserts for EZ and RS Calcium monotherapies.

PMDA's view:
The risk of adverse events requiring attention with Rosuzet is very similar to that of EZ and RS Calcium monotherapies, according to the submitted clinical study results and the results of the specified use-results survey of Zetia Tablets. Therefore, EZ + RS Calcium combination therapy would not pose additional safety concerns other than those for each monotherapy. At present, PMDA considers that the packaging insert for Rosuzet should include the same precautionary statements as those for EZ and RS Calcium monotherapies.

7.R.4.2 Use in patients with renal impairment

The applicant's explanation about the safety of Rosuzet in patients with renal impairment:
The incidence of adverse events in patients stratified by renal function in Studies P832 and P833 are summarized in Table 10.

Table 10. Incidence of adverse events by renal function category (SAS)

eGFR (mL/min/1.73 m^2)							
	EZ 10 mg (n = 35)	RS 2.5 mg (n = 72)	RS 5 mg (n = 71)	EZ 10 mg + RS 2.5 mg (n = 71)	EZ 10 mg + RS 5 mg (n = 72)	EZ 10 mg + RS 2.5 mg (n = 114)	EZ 10 mg + RS 5mg (n = 21)
30.0–59.9	60.0 (3/5)	0.0 (0/2)	60.0 (3/5)	33.3 (1/3)	20.0 (1/5)	68.8 (11/16)	33.3 (1/3)
60.0–89.9	30.4 (7/23)	34.5 (20/58)	43.9 (25/57)	46.2 (24/52)	37.7 (23/61)	73.8 (48/65)	83.3 (10/12)
≥90.0	14.3 (1/7)	41.7 (5/12)	22.2 (2/9)	25.0 (4/16)	50.0 (3/6)	72.7 (24/33)	83.3 (5/6)

% (number of patients)

The incidence of adverse events of EZ + RS Calcium combination therapy was similar to that of EZ or RS Calcium monotherapy, although this comparison is not rigorous because of the limited number of patients having 30.0 to 59.9 mL/min/1.73 m^2 of eGFR in both studies. There are no clinical study results of EZ + RS

Calcium combination therapy in patients with <30.0 mL/min/1.73 m^2 of eGFR, who were excluded from Studies P832 and P833. However, in a foreign clinical study (Study SHARP) of EZ 10 mg + simvastatin 20 mg combination therapy in >9000 patients with advanced or terminal chronic renal disease (median eGFR, 26.6 mL/min/1.73 m^2), no significant safety issues of EZ + statins combination therapy occurred (*Lancet* 2011;377:2181-92). Additionally, no clinically significant pharmacokinetic interactions were observed in EZ + RS Calcium combination therapy (new drug application data for Zetia Tablets). At present, considering these findings, the applicant judges that precautionary statements specific for Rosuzet are unnecessary for patients with renal impairment, and that the same precautionary statements as those for each of the active ingredients should be included in the packaging insert for Rosuzet.

PMDA's view:

According to the submitted clinical study data and the results of the specified use-results survey of Zetia Tablets, Rosuzet is unlikely to greatly increase the risk of adverse events compared with EZ or RS Calcium monotherapy in patients with renal impairment, and the risk of adverse events with Rosuzet would not greatly differ according to the patient's renal function level. At present, PMDA judges that precautionary statements for patients with renal impairment who receive Rosuzet should be the same as those for EZ and RS Calcium monotherapies.

7.R.4.3 Use in patients with hepatic impairment

The applicant's explanation about the safety of Rosuzet in patients with hepatic impairment:

Studies P832 and P833 enrolled patients whose ALT and AST at screening were ≤2 times the upper limit of the reference values at central laboratory, and excluded patients who had any of the contraindications listed in the packaging inserts for EZ and RS Calcium monotherapies (acute hepatitis, acute on chronic hepatitis, hepatic cirrhosis, hepatic cancer, or jaundice). The applicant categorized subjects in Studies P832 and P833 as "patients with hepatic impairment" if their baseline ALT, AST, or γ-GTP met the criteria for Grade ≥1 of hepatic impairment (≥1.25 times the upper limit of reference AST or ALT as well as ≥1.5 times the upper limit of reference γ-GTP value, or ≥2.5 times the upper limit of reference AST or ALT). In Study P832, no patients in the EZ + RS Calcium combination therapy group met the criterion. In Study P833, 4 patients in the EZ 10 mg + RS 2.5 mg group met the criterion, 3 of whom had adverse events (liver disorder and gastritis, nasopharyngitis, and gastritis), although the events were mild and unrelated to study treatment. Moreover, in the specified use-results survey of Zetia Tablets (12 weeks), incidence of adverse events tended to be higher in patients with hepatic impairment (n = 208) than those with no hepatic impairment (n = 948) in the EZ 10 mg + RS 2.5 mg group, the EZ 10 mg + RS 5 mg group, and the EZ 10 mg + other RS dose groups. The same tendency was observed in the EZ 10 mg monotherapy group. Among patients with hepatic impairment, adverse events did not greatly differ between those receiving EZ + RS combination therapy and those receiving EZ monotherapy.

Considering these results, the applicant judges that additional precautionary statements are unnecessary for patient with hepatic impairment who receive Rosuzet, and therefore the package insert Rosuzet will include the same precautionary statements as those for EZ and RS Calcium monotherapies.

PMDA's view:

On the basis of the submitted clinical study data and the results of the specified use-results survey of Zetia Tablets, patients with hepatic impairment did not tend to be at clearly more risk of having adverse events after treatment with Rosuzet as compared with EZ or RS Calcium monotherapy. At present, PMDA judges that precautionary statements for patients with hepatic impairment using Rosuzet should be the same as those used for EZ and RS Calcium monotherapies.

7.R.5 Post-marketing investigations

Post-marketing investigation is currently being discussed and its results and PMDA's conclusions will be reported in Review Report (2).

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

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

The new drug application data are currently being subjected to a document-based compliance inspection and data integrity assessment. The results and PMDA's conclusion are reported in Review Report (2).

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

The new drug application data are currently being subjected to an on-site GCP inspection. The results and PMDA's conclusion are reported in Review Report (2).

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

On the basis of the data submitted, PMDA has concluded that Rosuzet has superior efficacy than EZ and RS Calcium monotherapies in treatment of HC and FH and acceptable safety in view of its benefits, and therefore combining EZ 10 mg and RS 2.5 or 5 mg in a tablet is scientifically reasonable. Rosuzet is clinically meaningful because it offers a new treatment option for HC and FH patients. Further discussions are required for the clinical positioning of Rosuzet, the wording of precautionary statements in the packaging insert, and the post-marketing investigations.

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

Review Report (2)

February 8, 2019

Product Submitted for Approval

Brand Name	Rosuzet Combination Tablets LD
	Rosuzet Combination Tablets HD
Non-proprietary Name	Ezetimibe / Rosuvastatin Calcium
Applicant	MSD K.K.
Date of Application	May 22, 2018

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

At the Expert Discussion, the expert advisors supported PMDA's conclusions presented in Sections "7.R.1 "Clinical Significance of EZ / RS Calcium," "7.R.2 Dosage and administration," "7.R.3 Indications," and "7.R.4 Safety" in the Review Report (1).

PMDA also discussed the following points and took actions as necessary.

1.1 Risk management plan (draft)

PMDA's conclusion regarding the pharmacovigilance activities discussed in Section "7.R.5 Post-marketing investigations" in the Review Report (1):

In view of comments from the expert advisers at the Expert Discussion, PMDA considers that the applicant is not required to conduct additional pharmacovigilance activities, but should identify safety signals, if any, through regular pharmacovigilance activities.

- The scope of indications and dosage and administration of Rosuzet are within that of EZ and RS Calcium monotherapies.
- The combination of the active ingredients of Rosuzet, EZ and RS Calcium, has been widely used as a therapeutic option recommended by Japanese and foreign guidelines, with abundant clinical experience in Japanese patients.
- The post-marketing use-results surveys of EZ and RS Calcium monotherapies, have collected information from patients treated with EZ + RS Calcium combination therapy. This information and other data were reviewed during the re-examination process of both EZ and RS Calcium monotherapies, and no particular issues were identified.
- The potential risk of EZ + RS Calcium combination therapy in Studies P832 and P833 were similar to those observed in EZ and RS Calcium monotherapies. No additional concerns were raised for combination therapy with the 2 active ingredients.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for Rosuzet should include the safety specification presented in Table 11, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 12.

Table 11. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Rhabdomyolysis/myopathy • Hepatitis, hepatic function abnormal, jaundice • Hypersensitivity • Interstitial lung disease • Immune-mediated necrotizing myopathy • Platelet count decreased • Neuropathy peripheral • Erythema multiforme	None	None
Efficacy specification		
None		

Table 12. Summary of additional pharmacovigilance activities and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
None	• Prepare and provide information materials for healthcare professionals

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

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

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

The new drug application data (CTD 5.3.5.1.1, CTD 5.3.5.2.1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indications and dosage and administration under the condition shown below. The re-examination period is 4 years as the product is a new combination drug. The product is not classified as a biological product or a specified biological product. The drug product is not classified as a poisonous drug or a powerful drug.

Indications

Hypercholesterolemia, familial hypercholesterolemia

Dosage and Administration

The usual adult dosage is one tablet (10 mg/2.5 mg or 10 mg/5 mg of ezetimibe/rosuvastatin) administered orally once daily after meal.

Condition of Approval

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

Appendix

List of Abbreviations

ACS	Acute coronary syndrome
ALT	Alanine aminotransferase
APOA1	Apolipoprotein A1
AST	Aspartate aminotransferase
BA	Bioavailability
BE	Bioequivalence
CK	Creatine phosphokinase
CPP	Critical process parameter
CQA	Critical quality attribute
DMF	Drug Master File
eGFR	Estimated glomerular filtration rate
EZ	Ezetimibe
FAS	Full analysis set
FH	Familial hypercholesterolemia
GC	Gas chromatography
Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms	Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms (PMSB/ELD Notification No. 64 dated February 14, 2000; partially revised by Notification No. 0229-10 of PFSB/ELD, dated February 29, 2012)
Guideline for Bioequivalence Studies for Formulation Changes of Oral Solid Dosage Forms	Guideline for Bioequivalence Studies for Formulation Changes of Oral Solid Dosage Forms (PMSB/ELD Notification No. 67 dated February 14, 2000; partially revised by Notification No. 0229-10 of PFSB/ELD, dated February 29, 2012)
γ-GTP	Gamma-glutamyl transferase
HC	Hypercholesterolemia
hCETP	Human cholesterol ester transfer protein
HDL	High density lipoprotein
HeFH	Heterozygous familial hypercholesterolemia
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
HoFH	Homozygous familial hypercholesterolemia
HPLC	High performance liquid chromatography
ICH Q1E guideline	"Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003)
IR	Infrared spectrophotometry
JAS Guideline 2012	Japan Atherosclerosis Society (JAS) guidelines for prevention of atherosclerotic cardiovascular diseases 2012
[redacted]	[redacted]
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein-cholesterol
MedDRA	Medical Dictionary for Regulatory Activities
non-HDL	Non-high-density lipoprotein
NPC1L1	Niemann-Pick C1 Like 1
PCSK9	Proprotein convertase subtilisin/kexin type 9
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PT	Preferred term
QbD	Quality by Design
QSAR	Quantitative structure-activity relationship
RNA	Ribonucleic acid
RS	Rosuvastatin

siRNA	Small interfering RNA
SMQ	Standardized MedDRA query
Statins	Hydroxymethylglutaryl-CoA reductase inhibitors
TG	Triglyceride
TLC	Thin-layer chromatography