Citation: Clin Transl Sci (2019) 12, 704–712; doi:10.1111/cts.12677

ARTICLE

The Bioequivalence and Effect of Food on the Pharmacokinetics of a Fixed-Dose Combination Tablet Containing Rosuvastatin and Ezetimibe in Healthy Japanese Subjects

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Certain patient populations are unable to achieve the recommended low-density lipoprotein cholesterol goals with statin monotherapy alone. Such patients may benefit from concomitant therapy with ezetimibe (EZE) 10 mg added on to a statin. To this end, fixed-dose combination (FDC) tablets containing EZE 10 mg and rosuvastatin (ROS) 2.5 mg (EZE/ROS2.5) and EZE 10 mg and ROS 5 mg (EZE/ROS5) have been developed for treatment of hypercholesterolemia. The purpose of the series of clinical studies reported herein was to evaluate the potential food effect (MK-0653H, protocol 836 (P836)) and the bioequivalence between FDC and co-administration of EZE and ROS in healthy Japanese subjects under fasted and fed conditions (MK-0653H, protocol 835 (P835) and MK-0653H, protocol 846 (P846), respectively). These studies show there is no clinically relevant food effect on EZE exposure following single oral administration of the FDC EZE/ROS5 in healthy Japanese subjects; however, ROS exposure was decreased in the fed state under conditions used to evaluate the maximum food effect. Following single oral administration of individual ROS tablets under the same conditions, the magnitude of decrease in ROS exposure was comparable to that seen with FDC, suggesting that the effect of food on ROS exposure was similar between the FDC tablet and co-administration of individual EZE and ROS tablets. The FDC EZE/ROS5 was generally well tolerated in healthy Japanese subjects under fasted and fed conditions.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE SUBJECT?

☑ Fixed-dose combination (FDC) tablets containing ezetimibe (EZE) 10 mg and rosuvastatin (ROS) 2.5 mg (EZE/ROS2.5) and EZE 10 mg and ROS 5 mg (EZE/ROS5) have been developed for treatment of hypercholesterolemia.

WHAT DID THIS STUDY ADDRESS?

☑ This report describes the results of studies designed to evaluate the potential food effect and the bioequivalence between FDC and co-administered EZE + ROS in healthy Japanese subjects under fasted/fed conditions.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Following single dose EZE/ROS5, there was no clinically relevant effect of food on EZE exposure; however, ROS exposure decreased in the fed vs. fasted state. The effect of food on ROS pharmacokinetics (PKs) was similar between the FDC EZE/ROS5 and ROS5 treatments (P836 and P846 part 1). Taken together, these results demonstrate that the effect of food on ROS PK was not due to the FDC tablet formulation.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Patients taking co-administration of EZE and ROS can be switched to FDC EZE/ROS. The FDC EZE/ROS may contribute to clinical outcomes by improving adherence.

Atherosclerosis is a primary feature of coronary heart disease (CHD), the leading cause of mortality and a major cause of morbidity in the industrialized world.[1] Although there are multiple independent risk factors for development and progression of atherosclerosis, among the most important is hypercholesterolemia, and particularly increased concentrations of low-density lipoprotein cholesterol (LDL-C). An extensive body of data now exists demonstrating that serum cholesterol concentration is etiologically related to risk of atherosclerosis and CHD; in fact, the risk

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Received: April 18, 2019; accepted: June 21, 2019. doi:10.1111/cts.12677

of death from CHD has been shown to have a continuous and graded relation to total serum cholesterol concentration ≥ 180 mg/dL (≈ 4.68 mmol/l).[2] Lipid-lowering therapies, including diet and drugs, have been shown not only to slow the progression of coronary atherosclerosis and reduce the risk of coronary events, but even in some cases to lead to regression.[3] The 2016 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) Guideline, the 2013 American College of Cardiology (ACC)/American Hospital Association (AHA) Guideline, and the 2016 ACC Expert consensus decision in the United States mentioned that, due to the abundance of evidence from large-scale studies conducted with the statins, the use of statins is recommended as drug treatment for atherosclerotic cardiovascular disease.[4–6] Current Japan Atherosclerosis Society (JAS) Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2017 (JAS 2017)[7] recommend the use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (hereinafter referred to as "statins") as first-line therapy for the treatment of hypercholesterolemia. Certain patient populations are unable to achieve the JAS recommended LDL-C goals with statin monotherapy alone.[8] Thus, the 2017 JAS guidelines mention that concomitant therapy with ezetimibe (EZE) 10 mg added on to a statin can be used to prevent the occurrence of atherosclerosis in high-risk patients with acute coronary syndrome.[7] EZE has a different mechanism of action compared with statins and decreases LDL-C by inhibiting intestinal absorption of cholesterol.[9] Both EZE and statins have complementary mechanisms of actions and can be co-administered to achieve larger reductions in LDL-C vs. the respective monotherapies.[10,11] Results from the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) demonstrated that the addition of EZE to a statin provided further reductions in cardiovascular events compared with statin therapy alone in patients with acute coronary syndrome.[12]

Based on these results, fixed-dose combination (FDC) tablets containing EZE with either atorvastatin (ATV) 10 mg or 20 mg (EZE/ATV10 or EZE/ATV20) have been approved for use in Japan. Prior studies have shown that patient adherence to lipid-lowering therapies is generally poor relative to other cardiovascular therapies.[13] Therefore, combining both EZE and rosuvastatin (ROS), the most widely used statin monotherapy, in a single tablet may improve patient adherence to medication and enable more patients to reach their LDL-C goals. Thus, FDC tablets containing EZE 10 mg and ROS 2.5 mg (EZE/ROS2.5) or EZE 10 mg and ROS 5 mg (EZE/ROS5) have been developed and approved for treatment of hypercholesterolemia for Japanese patients. The bioequivalence between FDC and co-administration of EZE and ROS under fasted conditions has been demonstrated. The Japanese package circular for marketed EZE 10 mg tablets advises that the product should be administered following the ingestion of a meal. The package circular for marketed ROS tablets indicates 20% and 6% decreases in maximum concentration (C_{max}) and area under the concentration-time curve (AUC) in the fed state by comparison to that of fasted state, respectively, and administration instructions state that ROS can be dosed regardless of food. Therefore, consistent with the instructions related to EZE, it was anticipated that EZE/ROS FDC should be administered following a meal.

The guideline "Clinical Pharmacokinetic Studies for Drugs"[14] recommends "absorption of drug substances from the digestive tract is likely to be affected by the presence of food or contents of the food. Therefore, if the clinical administration of a test drug is oral, effects of food on absorption from the digestive tract need to be investigated." According to this guideline, a food effect study of FDC is conducted.[14] However, several published and unpublished clinical and preclinical studies[15–17] suggest that exposure to ROS is lower under fed conditions as compared with fasted conditions. The purpose of the series of clinical studies reported herein was to evaluate the potential food effect (MK-0653H, protocol 836 (P836)) and the bioequivalence between FDC and co-administration of EZE and ROS in healthy Japanese subjects under fasted and fed conditions (MK-0653H, protocol 835 (P835) and MK-0653H, protocol 846 (P846), respectively).

METHODS

Patients and study design

All three studies (Merck, Kenilworth, NJ, protocol numbers P835, P836, and P846) were phase I, randomized, open-label, single-dose, two-period crossover studies conducted in accordance with "Clinical Pharmacokinetic Studies for Drugs" guidance[14]; **Figure S1**). Adult healthy Japanese men, nonsmoking, between 20 and 55 years of age, with a body mass index of 18.5–25 kg/m^2 were enrolled in these studies.

These studies were conducted between June 2015 and June 2017 in accordance with Good Clinical Practice and the ethical principles of the current Declaration of Helsinki. The protocols were approved by local institutional review boards and all subjects signed informed consent prior to the conduct of any study procedures.

The objectives for each of the studies were as follows: P835, to evaluate the bioequivalence between co-administered EZE + ROS and FDC EZE/ROS under fasted conditions in unconjugated EZE and ROS C_{max} and area under the concentration-time curve from time 0 to last measurable time point ($AUC_{0–last}$); P836, to examine the potential effect of food on the pharmacokinetics (PKs; unconjugated and total EZE and ROS C_{max} and $AUC_{0–last}$) of FDC EZE/ROS; P846, in part 1 to determine the potential effect of food on ROS PK (ROS C_{max} and $AUC_{0–last}$) after administration of a single oral dose of ROS tablet alone, and in part 2 to determine the bioequivalence of co-administered EZE + ROS and FDC EZE/ROS under fed conditions in unconjugated EZE and ROS C_{max} and area under the concentration-time curve from 0–72 hours postdose ($AUC_{0–72\ hr}$).

Study treatments

All subjects were admitted to the clinical site 1 day before study treatment in all periods and remained domiciled until the 48-hour postdose sample collection was completed. The order in which subjects received treatments orally (treatment A followed by treatment B, or treatment B followed by treatment A) within a given treatment period was randomly assigned according to a computer-generated

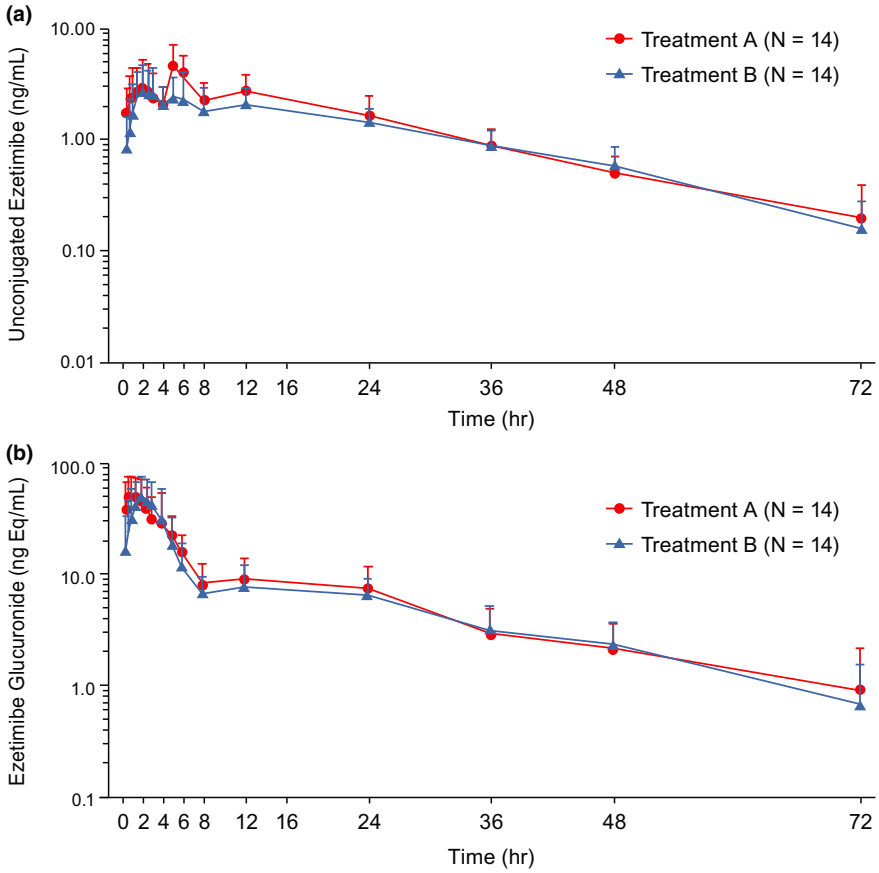

Figure 1 Mean concentration-time curves of unconjugated ezetimibe (EZE) and EZE glucuronide following single oral administration of fixed-dose combination (FDC) under fasted or fed conditions (P836). (**a**) Arithmetic mean plasma concentration-time profiles of unconjugated EZE in healthy Japanese male subjects after single oral administration of EZE/rosuvastatin 10 mg/5mg (EZE/ROS5) FDC tablets under fed or fasted conditions (mean + SD)—log liner plot. (**b**) Arithmetic mean plasma concentration-time profiles of ezetimibe glucuronide in healthy Japanese male subjects after single oral administration of EZE/ROS5 FDC tablets under fed or fasted conditions (mean + SD). Treatment A: EZE/ROS5 FDC tablets in the fasted state. Treatment B: EZE/ROS5 FDC tablets following a standard Japanese breakfast.

allocation schedule. There was a minimum 14-day (7 days for P846 part 1) washout between study drug administrations in each treatment period in consideration of the apparent elimination half-lives of EZE and ROS.

In each treatment period, subjects were fasted overnight for at least 10 hours and 4 hours after drug administration. In each study, Treatment A and B are as shown in **Table 1**. A standard Japanese breakfast (low-fat meal) was provided 30 minutes prior to drug administration and was consumed in its entirety within 20 minutes.

Sample collection

Plasma sampling for unconjugated EZE, total EZE, and ROS concentration measurements was performed from predose to 72 hours postdose at protocol defined time points (i.e., predose, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 24, 36, 48, and 72 hours postdose).

PK analyses

Measurement of unconjugated EZE, EZE glucuronide, and ROS concentrations in the plasma. The plasma concentrations of unconjugated EZE, total EZE (unconjugated + conjugated), and ROS were measured using a validated liquid chromatography with tandem mass spectrometry detection method. The assay had a lower limit of quantitation of 40 pg/mL for EZE, 200 pg/mL for total EZE, and 20 pg/mL for ROS, and calibration curves covered the concentration ranges of 40–10,000 pg/mL for EZE, 200–200,000 pg/mL for total EZE, and 20–25,000 pg/mL for ROS.

The plasma concentrations of EZE glucuronide conjugate were expressed as an equivalent concentration of unconjugated EZE and calculated for each plasma sample. This value was derived by subtracting the plasma concentration of unconjugated EZE from the corresponding total EZE concentration as equivalent concentration of EZE, because it could not be measured directly.

PK parameters estimated. The PK parameter values of EZE, EZE conjugate, and ROS for each subject were calculated using noncompartment analysis, based on the actual sampling times. The AUC_{0-last}, $AUC_{0-72\ hr}$, AUC estimated from time 0 to infinity ($AUC_{0-\infty}$), C_{max}, time to reach maximum concentration (T_{max}), and elimination half-

Table 1 Study design

Protocol number	P835	P836	P846 Part 1	P846 Part 2
Study design				
Treatment A	Single oral dose of FDC tablet under fasted conditions	Single oral dose of FDC EZE/ROS5 administered in the fasted state	Treatment A = single oral dose of ROS 5 mg tablet under the fasted state	Single oral dose of FDC EZE/ROS5 tablet following a standard Japanese breakfast[a]
Treatment B	Single oral co-administration of 1 EZE 10 mg tablet and 1 ROS 5 mg tablet under fasted conditions	Single oral dose of FDC EZE/ROS5 administered following the ingestion of a standard Japanese breakfast[a]	Single oral dose of ROS 5 mg tablet following a standard Japanese breakfast[a]	Single oral co-administration of 1 EZE 10 mg tablet and 1 ROS 5 mg tablet following a standard Japanese breakfast[a]

EZE, ezetimibe 10 mg; EZE/ROS5, ezetimibe/rosuvastatin 10 mg/5 mg; FDC, fixed-dose combination; ROS, rosuvastatin.
[a]Total fat: 8.5 g; total carbohydrates: 85.3 g; total protein: 35.8 g; total calories: 571 kcal.

life ($t_{1/2}$) of plasma unconjugated EZE, EZE glucuronide, and ROS after single oral dose of FDC tablet with or without a standard Japanese breakfast were estimated in healthy Japanese subjects. Phoenix WinNonlin version 6.3 (Certara, Princeton, NJ) was used for PK parameter calculation.

Statistical analysis

Sample size calculation. In P835, a total of 116 enrolled subjects was anticipated to result in 110 completers, which would provide 80% power to show that the 90% confidence intervals (CIs) of the geometric mean ratios (GMRs) of all four primary end points were contained within (0.80–1.25). The calculations were based on the assumptions that the true GMRs would be 0.90 for all of the 4 end points and the true within-subject SDs would be 0.223 (ln ng·hour/mL) and 0.316 (ln ng/mL) for AUC_{0-last} and C_{max} of unconjugated EZE, and 0.1889 (ln ng·hour/mL) and 0.2679 (ln ng/mL) for AUC_{0-last} and C_{max} of ROS, respectively.

In P836, a total of 14 enrolled subjects were expected to result in 12 completers, which would result in half-widths of the 90% CIs of the GMRs of 0.14 and 0.20 for AUC_{0-last} and C_{max} of unconjugated EZE, 0.12 and 0.18 for AUC_{0-last} and C_{max} of total EZE, and 0.12 and 0.16 for AUC_{0-last} and C_{max} of ROS, respectively (all on the natural log scale), under the within-subject SD estimates of 0.184 (ln ng·hour/mL) and 0.272 (ln ng/mL) for AUC_{0-last} and C_{max} of unconjugated EZE, 0.162 (ln ng·hour/mL) and 0.241 (ln ng/mL) for AUC_{0-last} and C_{max} of total EZE, and 0.157 (ln ng·hour/mL) and 0.220 (ln ng/mL) for AUC_{0-last} and C_{max} of ROS, respectively. The resulting 90% CIs of the GMRs were expected to be (0.87–1.15) and (0.82–1.22) for the AUC_{0-last} and C_{max} of unconjugated EZE, (0.89–1.13) and (0.84–1.20) for the AUC_{0-last} and C_{max} of total EZE, and (0.89–1.12) and (0.85–1.18) for the AUC_{0-last} and C_{max} of ROS, respectively, if the point estimates of the GMRs were all 1.00.

In P846 part 1, a total of 14 enrolled subjects were expected to result in half-widths of the 90% CIs of the GMRs of 0.15 and 0.18 on the natural log scale for AUC_{0-last} and C_{max} of ROS, respectively, under the within-subject SD estimates of 0.23 (ln ng·hour/mL) and 0.27 (ln ng/mL), respectively. The resulting 90% CIs of the GMRs were expected to be (0.86–1.17) and (0.83–1.20) for the AUC_{0-last} and C_{max} of ROS, respectively, if the point estimates of the GMRs were both 1.00.

In P846 part 2, a total of 120 enrolled subjects were anticipated to provide ~ 89% power to show that the 90% CIs of the GMRs of the all 4 primary end points were contained within (0.80–1.25). The calculations were based on the assumptions that the true GMRs would be 0.90 for all of the 4 end points and the true within-subject SDs would be 0.18 (ln ng·hour/mL) and 0.28 (ln ng/mL) for $AUC_{0-72\,hr}$ and C_{max} of unconjugated EZE, and 0.23 (ln ng·hour/mL) and 0.27 (ln ng/mL) for $AUC_{0-72\,hr}$ and C_{max} of ROS, respectively.

PKs. AUC and C_{max} were natural log-transformed and analyzed using separate linear mixed-effects models with treatment and period as fixed effects. An unstructured covariance matrix was used to model correlation between treatments. Ninety percent CIs of GMRs were calculated using the above model. Descriptive statistics were calculated for the other parameters.

Safety. The safety and tolerability were assessed through the following prespecified safety parameters: physical examinations, vital signs, blood pressure, adverse events (AEs), and routine hematology, chemistry, and urinalysis surveillance. Laboratory safety measurements included alanine aminotransferase, aspartate aminotransferase, and creatine kinase. AEs were tabulated by treatment. Changes from baseline in vital sign and laboratory parameters were calculated by treatment.

RESULTS

Disposition of patients

All studies enrolled healthy Japanese men (**Table 2**). A total of 268 subjects were enrolled across the three studies, and five subjects discontinued treatment before study end. The demographic characteristics were generally well balanced across the studies.

PKs

EZE PK. In the food effect study (P836), the arithmetic mean plasma concentration-time profiles for unconjugated EZE and EZE glucuronide were similar in the fasted and fed states following single oral administration of FDC EZE/

Table 2 Subject background

			P846	
Protocol number	**P835**	**P836**	**Part 1**	**Part 2**
Male, *N*	118	14	14	122
Mean age, years	39.2	27.5	34.71	35.64
Age range, years	20–55	20–38	22–47	20–55
BMI, kg/m^2	21.90	21.85	21.72	21.82
Completed, *N*	116	14	14	119
Discontinued, *N*	2	0	0	3
AE	1	-	-	2
Lost to follow-up	1	-	-	1

AE, adverse event; BMI, body mass index.

ROS5 tablets in healthy Japanese subjects (**Figure 1**). The GMRs (fed/fasted) of AUC_{0-last}, C_{max}, and $AUC_{0-\infty}$ for unconjugated EZE were 0.85 (90% CI = 0.76–0.95), 0.84 (0.73–0.96), and 0.82 (0.72–0.94), respectively; 0.92 (0.84–1.01), 1.05 (0.91–1.21), and 0.91 (0.82–1.02) for EZE glucuronide, respectively (**Table 3**). In general, the median T_{max}, mean $t_{1/2}$, and distribution of T_{max} and $t_{1/2}$ were comparable for unconjugated EZE and EZE glucuronide under fed and fasted conditions (**Table S1**).

The PK results of the bioequivalence studies (i.e., P835 and P846 part 2) following administration of a single oral dose of the FDC EZE/ROS5 and co-administration EZE 10 mg and ROS 5 mg individual tablets under fasted and fed conditions are shown in **Table 3**. In P835, the GMRs (FDC/co-administration) for unconjugated EZE were 0.99 (90% CI = 0.96–1.02) for $AUC_{0-72\ hr}$ and 1.01 (0.95–1.07) for C_{max}. In P846, the GMRs (FDC/co-administration) for unconjugated EZE were 0.98 (90% CI = 0.95–1.01) for $AUC_{0-72\ hr}$ and 0.99 (0.94–1.05) for C_{max}. The 90% CIs of GMRs for both $AUC_{0-72\ hr}$ and C_{max} of unconjugated EZE were all contained within the prespecified bioequivalence bounds (0.80–1.25), indicating that the FDC tablet is bioequivalent to co-administered EZE 10 mg and ROS 5 mg under fasted and fed conditions.

ROS PK. In the P836 study, ROS exposure was decreased following the administration of a single oral dose of EZE/ROS5 FDC under fed vs. fasted conditions (**Figures 2 and 3 and Table 4**). The GMRs (fed/fasted) of AUC_{0-last}, C_{max}, and $AUC_{0-\infty}$ for ROS were 0.48 (90% CI = 0.41–0.56), 0.38 (0.31–0.46), and 0.44 (0.34–0.57), respectively. The median T_{max}, mean $t_{1/2}$, and distribution of T_{max} and $t_{1/2}$ were comparable for ROS under fed and fasted conditions.

In part 1 of study P846, all subjects demonstrated a decrease in C_{max} and AUC under the fed compared with the fasted state following the administration of a single oral dose of ROS5 (**Figures 2 and 3 and Table 4**). The GMR (fed/fasted) for ROS was 0.44 (90% CI = 0.40–0.49) for AUC_{0-last}, 0.33 (0.30–0.37) for C_{max}, and 0.45 (0.40–0.51) for $AUC_{0-\infty}$. In general, the median T_{max}, mean $t_{1/2}$, and distribution of T_{max} and $t_{1/2}$ were comparable for ROS between the fed and the fasted states, respectively (**Table S2**).

Although the concentration of ROS decreased under fed conditions following the administration of EZE/ROS5 FDC (P836) or ROS5 alone (P846), both treatments were bioequivalent under these conditions (**Table 4**). Under fed conditions, the GMRs (FDC/co-administration) for ROS were 1.04 (90% CI = 1.01–1.07) for $AUC_{0-72\ hr}$ and 1.01 (0.97–1.05) for C_{max} (**Table 4**). Under fasted conditions, the GMRs (FDC/co-administration) were 0.99 (90% CI = 0.96–1.02) for $AUC_{0-72\ hr}$ and 1.01 (0.95–1.07) for C_{max}. The 90% CIs of GMR for both $AUC_{0-72\ hr}$ and C_{max} of ROS were contained within the prespecified bioequivalence bounds (0.80–1.25).

Table 3 PK parameter values for EZE (unconjugated) under fed and fasted conditions following single oral administration of FDC or co-administration of EZE + ROS5

		FDC			Co-administration			FDC/co-administration	
Study	**PK parameter**	***N***	**GM**	**95% CI**	***N***	**GM**	**95% CI**	**GMR**	**90% CI**
P835 (fasted)	$AUC_{0-72\ hr}$ (ng·hour/mL)	117	76.4	71.2–81.9	117	77.2	71.6–83.2	0.99	0.96–1.02
	C_{max} (ng/mL)	117	4.73	4.32–5.18	117	4.69	4.29–5.13	1.01	0.95–1.07
P846 part 2 (fed)	$AUC_{0-72\ hr}$ (ng·hour/mL)	120	86.8	81.8–92.2	120	88.7	83.1–94.6	0.98	0.95–1.01
	C_{max} (ng/mL)	120	4.93	4.52–5.37	120	4.96	4.56–5.39	0.99	0.94–1.05

		Fasted			Fed			Fed/fasted	
Study	**PK parameter**	***N***	**GM**	**95% CI**	***N***	**GM**	**95% CI**	**GMR**	**90% CI**
P836	AUC_{0-last} (ng·hour/mL)	14	83.2	68.9–100	14	70.7	58.7–85.1	0.85	0.76–0.95
	C_{max} (ng/mL)	14	4.49	3.29–6.14	14	3.76	2.87–4.92	0.84	0.73–0.96
	$AUC_{0-\infty}$ (ng·hour/mL)	14	91.7	74.2–113	14	75.2	62.7–90.1	0.82	0.72–0.94

$AUC_{0-72\ hr}$, area under the concentration-time curve from time 0–72 hours postdose; AUC_{0-last}, area under the concentration-time curve from time 0 to last measurable time point; $AUC_{0-\infty}$, area under the concentration-time curve estimated from time 0 to infinity; C_{max}, maximum concentration; CI, confidence interval; EZE, ezetimibe 10 mg; EZE + ROS5, ezetimibe 10 mg + rosuvastatin 5 mg; FDC, fixed-dose combination; GM, geometric mean; GMR, geometric mean ratio; PK, pharmacokinetic.
P835: To evaluate bioavailability between FDC and co-administration in the fasted state. P846 part 2: To evaluate bioavailability between FDC and co-administration in the fed state. P836: To evaluate the food effect on FDC (EZE).

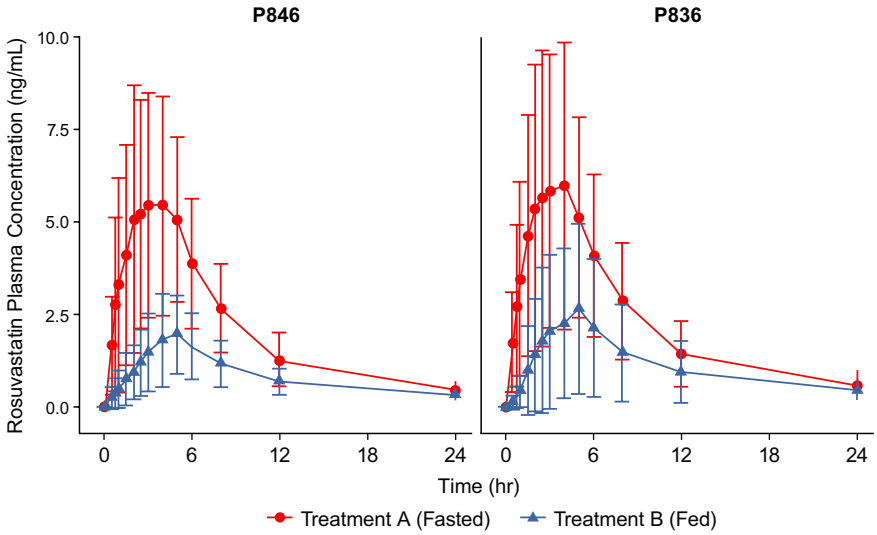

Figure 2 Mean concentration-time curves of rosuvastatin following single oral administration of ezetimibe/rosuvastatin 10 mg/5 mg (EZE/ROS5) fixed-dose combination (FDC) tablets under fasted or fed conditions (mean ± SD). P836: Japan marketed rosuvastatin 5 mg (n = 14). P846: EZE/ROS5 FDC (n = 14).

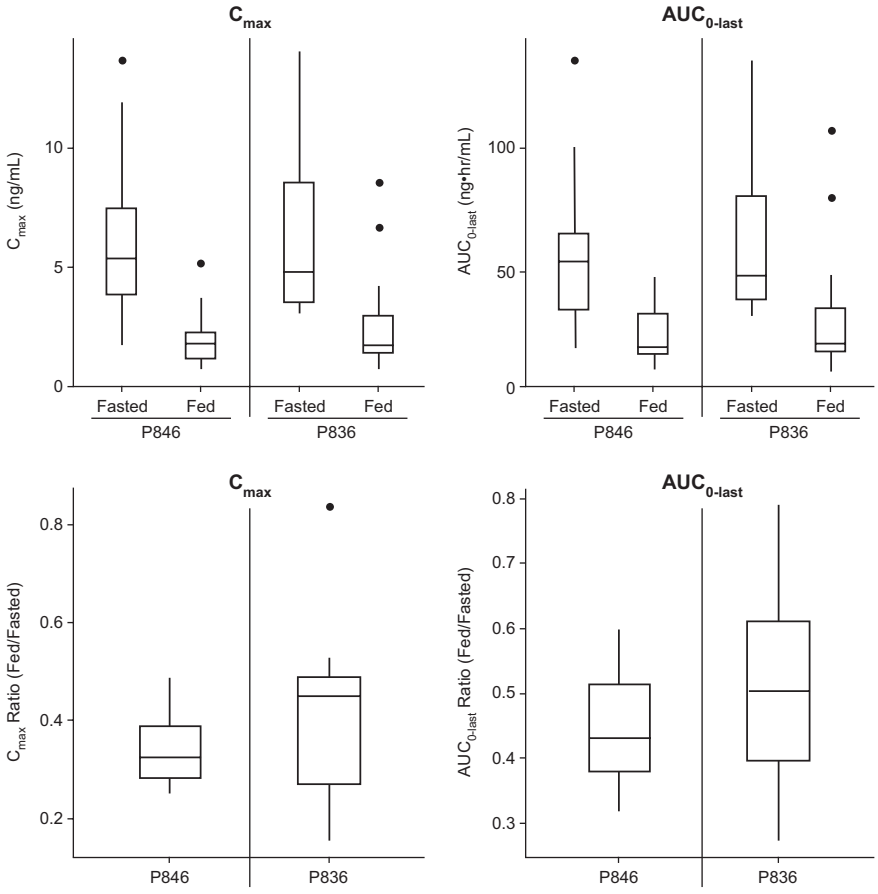

Figure 3 Comparison of pharmacokinetic (PK) parameter values and comparison of food effect on rosuvastatin (ROS) PK. P846: Japan marketed ROS5. P836: EZE/ROS5 FDC. Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th and 95th percentiles. Plots show data points outside this range. AUC_{0-last}, area under the concentration-time curve from time 0 to last measurable time point; C_{max}, maximum concentration.

Table 4 PK parameter values for ROS under fed and fasted conditions following single oral administration of FDC or co-administration of EZE + ROS5

		FDC			Co-administration			FDC/co-administration	
Study	**PK parameter**	***N***	**GM**	**95% CI**	***N***	**GM**	**95% CI**	**GMR**	**90% CI**
P835[a] (fasted)	$AUC_{0-72\ hr}$ (ng·hour/mL)	117	54.9	51.1–58.9	117	54.7	50.8–58.9	1.00	0.97–1.03
	C_{max} (ng/mL)	117	6.58	6.09–7.11	117	6.67	6.17–7.22	0.99	0.95–1.03
P846[b] part 2 (fed)	$AUC_{0-72\ hr}$ (ng·hour/mL)	120	28.3	26.3–30.4	120	27.3	25.2–29.5	1.04	1.01–1.07
	C_{max} (ng/mL)	120	2.39	2.20–2.60	120	2.37	2.18–2.57	1.01	0.97–1.05

		Fasted			Fed			Fed/fasted	
Study	**PK parameter**	***N***	**GM**	**95% CI**	***N***	**GM**	**95% CI**	**GMR**	**90% CI**
P836[c]	AUC_{0-last} (ng·hour/mL)	14	55.9	41.6–75.1	14	27.0	18.6–39.3	0.48	0.41–0.56
	C_{max} (ng/mL)	14	5.47	3.89–7.46	14	2.07	1.39–3.09	0.38	0.31–0.46
	$AUC_{0-\infty}$ (ng·hour/mL)	14	65.1	44.7–94.9	14	28.4	19.6–41.2	0.44	0.34–0.57
P846[b] part 1	AUC_{0-last} (ng·hour/mL)	14	51.0	38.2–68.0	14	22.4	16.9–29.7	0.44	0.40–0.49
	C_{max} (ng/mL)	14	5.36	3.89–7.38	14	1.79	1.29–2.49	0.33	0.30–0.37
	$AUC_{0-\infty}$ (ng·hour/mL)	14	52.6	39.8–69.4	14	23.9	18.3–31.1	0.45	0.40–0.51

$AUC_{0-72\ hr}$, area under the concentration-time curve from time 0–72 hours postdose; AUC_{0-last}, area under the concentration-time curve from time 0 to last measurable time point; $AUC_{0-\infty}$, area under the concentration-time curve estimated from time 0 to infinity; C_{max}, maximum concentration; CI, confidence interval; EZE + ROS5, ezetimibe 10 mg + rosuvastatin 5 mg; FDC, fixed-dose combination; GM, geometric mean; GMR, geometric mean ratio; PK, pharmacokinetic; ROS, rosuvastatin 5 mg.
[a]P835: To evaluate bioavailability between FDC and co-administration in the fasted state. [b]P846 part 2: To evaluate bioavailability between FDC and co-administration in the fed state. [c]P836: To evaluate the food effect on FDC (ROS).

Safety. A total of 268 subjects were included in the assessment of safety and tolerability in these three studies. Across these studies, 13 subjects reported a total of 12 AEs. The reported AEs were influenza, alanine aminotransferase increased, aspartate aminotransferase increased, creatine kinase increased, white blood cell increased, diarrhea, headache, eczema nummular, nasopharyngitis, arthropod sting, hematuria, and tooth repair. Three subjects discontinued study medication due to AEs, influenza (P835, co-administration in fasted), nasopharyngitis (P846 part 2, co-administration in fed), and hematuria (P846 part 2, FDC in fed). All adverse experiences were mild or moderate in intensity and resolved by follow-up except hematuria.

DISCUSSION

FDC tablets containing EZE 10 mg and ROS 2.5 mg or 5 mg have been developed and approved for the treatment of hypercholesterolemia in Japan. The 5 mg dose of ROS was used in these PK studies because it is the highest dose of ROS used in the FDC clinical development program and should enable more robust detection of possible PK perturbances. Two clinical trials were performed to assess the bioequivalence of FDC EZE/ROS5 with co-administered EZE 10 mg and ROS5 mg as separate tablets and to evaluate the effect of food on EZE and ROS PK in healthy male Japanese subjects.

In studies P835 and P846 part 2, the bioequivalence between Japanese marketed products EZE10/ROS5 and FDC EZE/ROS5 were demonstrated. When the FDC EZE/ROS5 tablets were administered under both fasted and fed conditions, the PK of EZE and ROS were equivalent to that seen following co-administration of EZE 10 mg + ROS 5 mg as individual tablets.

Following single dose administration of EZE/ROS5, there was no clinically relevant effect of food on EZE exposure; however, ROS exposure was decreased in the fed state as compared with fasted conditions (P836). The effect of food on ROS PK was similar between the treatments of FDC EZE/ROS5 and individual ROS 5 mg tablets (P836 and P846 part 1). Taken together, these results demonstrate that the effect of food on ROS PK was not due to the unique formulation of the FDC under evaluation in these studies. The studies discussed in this report (i.e., P836 and P846 part 1) were designed as conventional food effect studies. Both EZE/ROS5 FDC and ROS5 alone were administered 10 hours after the ingestion of a meal with fasting over 4 hours postdose to maximize the evaluation of the effect of food on absorption.

The Japanese package circular of individual ROS products states that there is no effect of food on the absorption of ROS and provides guidance for dosing without regard to meals.[18] This statement is based on a published clinical study evaluating ROS PK following repeated once-daily oral administration for 14 days, within 3 hours after the ingestion

of a dinner (i.e., the fasted condition), and 15 minutes after the ingestion of a dinner (i.e., the fed condition; composition of meal was not reported). In that study, GMR between fed and fasted of C_{max} and AUC of ROS decreased by 20% and 6%, respectively, in non-Japanese healthy subjects (n = 20). In addition, food intake is unlikely to compromise the LDL-C–lowering effect of ROS and the clinical response for EZE/ROS FDC would be expected to be similar regardless of the ingestion of a meal.[18] Hence, administration instructions state that ROS can be dosed regardless of food. The Japanese package circular for marketed EZE 10 mg tablets advises that the product should be administered following the ingestion of a meal. Therefore, consistent with the instructions related to EZE, it was anticipated that EZE/ROS FDC should be administered following a meal.

These differences in ROS PK observed between FDC and individual ROS tablets can be attributed to differences in the study designs. Several prior reports demonstrated a decrease in ROS exposure under fed conditions single-dose administration following an overnight fast in clinical and nonclinical studies.[15–17] McLean *et al*.[15] demonstrated that the exposure (C_{max} and $AUC_{0-\infty}$) of ROS decreased by 40% to 42% after a low-fat meal and 30% to 35% after a high-fat meal compared with fasted conditions, in a clinical study of single oral administration of ROS 10 mg to healthy white (n = 14) and East Asian (n = 13) subjects. In this study, the LDL-C–lowering effect by ROS was not different between fed and fasted conditions, even though the ROS exposure was lower under fed conditions.[15] In another study, although the formulation was different, it was reported that the ROS exposure (C_{max} and area under concentration-time profiles (AUC_{0-t})) in healthy Chinese subjects (n = 12) under fed conditions was extremely low compared with that observed under fasted conditions, following single oral administration of ROS 10 mg.[17] Taken together, these studies indicate that ROS exposure potentially decreases under fed conditions compared with strict fasting conditions, single-dose administration, and morning administration.

There is a limitation that should be considered when evaluating the results of these PK studies. There have been no efficacy studies performed in patients with hypercholesterolemia receiving FDC EZE/ROS or individual ROS under fasted conditions. A dose-finding study of ROS in Japanese patients was reported wherein ROS was administered 3 hours after dinner.[19] Although the LDL-C–lowering effect in that study was dose-dependent, there was no evidence of a correlation between exposure and efficacy.

In the 2016 National Health and Nutrition Survey in Japan, the proportions of patients who abstained from eating breakfast in the morning were 6.1% for men and 3.2% for women.[20] The anticipated patient population for this drug includes patients with hypercholesterolemia who do not adequately respond to diet/exercise therapy and single-agent pharmacotherapy. Therefore, these patients will be treated according to the Guideline for the Prevention of Lipid Abnormalities for Arterial Sclerotic Disorders 2013. In this document, it states "keep having breakfast, lunch, and dinner at regular hours." Considering these circumstances in Japan, the number of patients who take medication under fasted conditions in the morning and retain the fasted condition until noon is expected to be limited. Additionally, it has been reported that night dosing of statins is recommended for clinical ROS administration because peak hepatic 3-hydroxy-3-methylglutaryl coenzyme A reductive activity and cholesterol biosynthesis occurs at night.[21,22] Although the LDL-C–lowering effect following FDC administered under fasted conditions was not available, the LDL-C–lowering effect data under fed conditions can explain the efficacy in the majority of Japanese patients.

CONCLUSION

These results show there is no clinically relevant food effect on EZE exposure following single oral administration of the FDC EZE/ROS5 in healthy Japanese subjects; however, ROS exposure was decreased in the fed state under conditions used to evaluate the maximum food effect. Following single oral administration of individual ROS tablets under the same conditions, the magnitude of decrease in ROS exposure was comparable to that seen with FDC, suggesting that the effect of food on ROS exposure was similar between the FDC tablet and co-administration of individual EZE and ROS tablets. The FDC EZE/ROS5 was generally well tolerated in healthy Japanese subjects under fasted and fed conditions.

Supporting Information. Supplementary information accompanies this paper on the *Clinical and Translational Science* website (www.cts-journal.com).

Figure S1. Study design.
Table S1. PK parameter values for ezetimibe following single oral administration of FDC under fasted or fed states (P836).
Table S2. PK parameter values for rosuvastatin following single oral administration of FDC or Japan marketed ROS 5 mg under fasted or fed states (P836, P846 Part 1).

Acknowledgments. Medical writing and/or editorial assistance was provided by Amy Levonas and Michele McColgan. This assistance was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ. The authors thank Dr. Hiroyuki Yoshitsugu, of MSD K.K., Tokyo, Japan, for supervision of research. The authors thank Dr. Hisakuni Sekino, of Medical Corporation Hoeikai, Sekino Clinical Pharmacology Clinic, Tokyo, Japan, for conducting the P835 study and collection of the P835 data.

Funding. Funding for this research was provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ.

Conflict of Interest. C.N., Y.M., Ka.F, and M.S. are employees of MSD K.K., Tokyo, Japan, and may own stock and/or stock options in Merck & Co., Inc., Kenilworth, NJ. R.E.W. and M.O.B. are or were employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, and may own stock and/or stock options in Merck & Co., Inc., Kenilworth, NJ. Ke.F. reports grants from MSD K.K. Ke.F. also reports grants from Astellas Pharma Inc., AstraZeneca K.K., Fujiyakuhin Co., Ltd., Kissei Pharmaceutical Co., Ltd., Kyowa Hakko Kirin Co., Ltd., GlaxoSmithKline K.K., Daiichi Sankyo Company, Ltd., Taiho Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Chugai Pharmaceutical Co., Ltd., Eli Lilly Japan K.K., Nobelpharma Co., Ltd., Novartis Pharma K.K., Pfizer

Japan, Inc., Mochida Pharmaceutical Co., Ltd, Janssen Pharmaceutical K.K., Shionogi & Co., Ltd., Taisho Pharmaceutical Co., Ltd., Nippon Zoki Pharmaceutical Co., Ltd., outside the submitted work.

Author Contributions. C.N., Y.M., Ka.F., M.S., R.E.W., M.O.B., and Ke.F. wrote the manuscript. C.N., Y.M., Ka.F., M.S., R.E.W., and M.O.B. designed the research. C.N., Y.M., Ka.F., M.S., R.E.W., M.O.B., and Ke.F. performed the research. Y.M, M.S., and R.E.W. analyzed the data.

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