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ORIGINAL ARTICLE

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Effects of itraconazole and rifampicin on the single-dose pharmacokinetics of the nonsteroidal mineralocorticoid receptor blocker esaxerenone in healthy Japanese subjects

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Aims: To investigate the effects of the strong cytochrome P450 (CYP) 3A inhibitor itraconazole and the strong CYP3A inducer rifampicin on the pharmacokinetics of single-dose esaxerenone, a nonsteroidal mineralocorticoid receptor blocker, in healthy Japanese subjects.

Methods: Two open-label, single-sequence, crossover studies were conducted in healthy Japanese males aged 20–45 years. In Study 1 (n = 20), subjects received a single oral 2.5 mg dose of esaxerenone (Days 1, 13), with itraconazole 200 mg twice daily (Day 8) and once daily (Days 9–16). In Study 2 (n = 12), subjects received a single oral 5 mg dose of esaxerenone (Days 1, 13), with rifampicin 600 mg once daily (Days 8–16). The plasma concentration of esaxerenone and esaxerenone metabolites were measured using liquid chromatography–tandem mass spectrometry. Pharmacokinetic parameters were calculated using noncompartmental analysis, and safety was assessed.

Results: Esaxerenone exposure increased when coadministered with itraconazole. Geometric least-square mean ratios (90% confidence interval) of peak plasma esaxerenone concentration (C_{max}), area under the plasma concentration–time curve (AUC) from zero until the last measurable concentration (AUC_{last}) and AUC from zero until infinity (AUC_{inf}) were 1.13 (1.05, 1.20) ng mL^{-1}, 1.47 (1.40, 1.54) ng h mL^{-1} and 1.53 (1.45, 1.62) ng h mL^{-1}, respectively. Esaxerenone exposure decreased when coadministered with rifampicin. Geometric least-squares mean ratios (90% confidence interval) of esaxerenone C_{max}, AUC_{last} and AUC_{inf} were 0.659 (0.599, 0.724), 0.315 (0.300, 0.332) and 0.312 (0.297, 0.328), respectively.

Conclusion: Itraconazole increased esaxerenone AUC_{inf} by 53.1%, and rifampicin decreased esaxerenone AUC_{inf} by 68.8%. These results suggest that caution is

The authors confirm that the Principal Investigator for this paper is Masanari Shiramoto and that he had direct clinical responsibility for subjects.

recommended when coadministering esaxerenone with strong inhibitors and inducers of CYP3A.

KEYWORDS

CYP3A, drug–drug interactions, itraconazole, pharmacokinetics, rifampicin

1 | INTRODUCTION

Esaxerenone (CS-3150) is a nonsteroidal **mineralocorticoid receptor** (MR) blocker approved for the treatment of hypertension and in development for the treatment of diabetic nephropathy in Japan. Results from an *in vitro* study showed that esaxerenone possesses a favourable pharmacological profile relative to other MR blockers such as **spironolactone** and **eplerenone**.[1] The MR affinity of esaxerenone is 4- and 76-fold greater than that of eplerenone and spironolactone, respectively.[1] The half-maximal inhibitory concentration of esaxerenone for the transcriptional activity of human MR is 3.7 nM, and its potency was superior to that of spironolactone and eplerenone, whose half-maximal inhibitory concentrations were 66 and 970 nM, respectively.[1] The clinical efficacy of esaxerenone for essential hypertension was demonstrated in a recent double-blind phase 3 study,[2] in which esaxerenone 2.5 mg d^{-1} was shown to be noninferior to eplerenone 50 mg d^{-1}; furthermore, the esaxerenone 5 mg d^{-1} dosage was superior to the 2.5 mg d^{-1} dosage.[2] Both dosages of esaxerenone demonstrated efficacy in lowering blood pressure (BP) and were well tolerated.[2]

We have already characterised the pharmacokinetics (PK) of esaxerenone in several studies.[3,4] Esaxerenone has shown dose-proportionality after administration of single and multiple doses (5–200 mg in the single-dose study and 10–100 mg d^{-1} in the multiple-dose study) to healthy Japanese adult males with its time to reach maximum plasma concentration and terminal elimination half-life remaining relatively unchanged across the dose ranges of 2.5 to 3.5 hours and 18.7 to 22.9 hours, respectively.[3] Esaxerenone has a high absolute bioavailability of approximately 90%.[4]

Based on a mass balance study in healthy volunteers, most of the radioactivity of ^{14}C-labelled esaxerenone was excreted as metabolites in faeces and urine, with proportions of unchanged drug of 18.7 and 1.6%, respectively.[5] Thus, the main elimination route of esaxerenone is via metabolism, and it has been suggested that oxidation, glucuronic acid conjugation and hydrolysis are involved.[5] Esaxerenone metabolites include oxidised metabolite (M1), *O*-glucuronide conjugate (M4) and acyl-glucuronide (M11), which are formed by cytochrome P450 3A (CYP3A), 5′-diphospho-glucuronosyltransferase (UGT) and hydrolysis followed by glucuronidation, respectively.

In vitro metabolism studies using human liver microsomes and a human CYP expression system showed that **CYP3A4** and CYP3A5 are involved in the oxidative metabolism of esaxerenone and no metabolites are produced by other major P450 isoforms.[5] Based on metabolite profiles in faeces and urine, it was estimated that the overall excretion rate of oxidised metabolites, the production of which is catalysed by CYP3A, was about 30% of the total dose.[5] Additionally, esaxerenone is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein *in vitro*,[5] but given an absolute bioavailability of approximately 90%,[4] these transporters do not appear to play an important role in esaxerenone absorption. Consequently, the effect of concomitant administration of P-gp modulators on esaxerenone PK is likely to be limited. However, there is potential for esaxerenone exposure to vary when coadministered with inhibitors/inducers of CYP3A, as about 1/3 of the clearance of esaxerenone appears to be through oxidative metabolism by CYP3A.

The MR blocker eplerenone is mainly metabolised via the CYP3A4 pathway, and it has been reported that inhibitors of CYP3A4,

What is already known about this subject

- Esaxerenone, a nonsteroidal mineralocorticoid receptor blocker, has demonstrated clinical efficacy and safety in the treatment of hypertension.
- Esaxerenone is eliminated via multiple pathways, including oxidation, glucuronidation and hydrolysis.
- The contribution of CYP3A-mediated oxidation to esaxerenone clearance is approximately 30%, as indicated by the excretion ratio of oxidised metabolites into urine and faeces.

What this study adds

- Itraconazole, a strong CYP3A inhibitor, increased esaxerenone AUC_{inf} by approximately 1.5-fold, compared with administration of esaxerenone alone, which was caused by inhibition of oxidative metabolism of esaxerenone.
- Rifampicin, a strong CYP3A inducer, reduced esaxerenone AUC_{inf} by approximately 0.3-fold, compared with administration of esaxerenone alone, which was caused by induction of oxidative metabolism and glucuronidation of esaxerenone.
- These results suggest that caution is recommended when esaxerenone is coadministered with a strong inhibitor or inducer of CYP3A in patients with hypertension.

such as ketoconazole, erythromycin, saquinavir, verapamil and fluconazole, can cause 2- to 5-fold increases in eplerenone drug exposure.[6] Concomitant use of eplerenone with strong CYP3A inhibitors, such as itraconazole, is therefore contraindicated, and dose adjustment is necessary when moderate CYP3A inhibitors are coadministered with eplerenone.[6–8]

Thus, it is important to evaluate the effects of CYP3A inhibitors and inducers on the PK of the novel MR blocker esaxerenone. Itraconazole, a strong inhibitor of CYP3A, and rifampicin, a strong inducer of CYP3A, are agents often used in drug–drug interaction (DDI) studies. Thus, expanding on our previously published PK studies,[3,4] this paper reports the results of 2 esaxerenone DDI studies conducted in healthy Japanese subjects: Study 1 investigated the effect of multiple doses of itraconazole on esaxerenone PK following a single dose; and Study 2 investigated the effect of multiple doses of rifampicin on esaxerenone PK following a single dose. Given that rifampicin has the ability to induce not only CYP3A, but also UGT, the plasma concentrations of esaxerenone metabolites—M1, M4 and M11—were also evaluated in Study 2.

2 | METHODS

2.1 | Study design and treatments

Studies 1 and 2 were both single-centre, open-label, single-sequence, crossover studies. Both studies received institutional review board approval (Hakata Clinic Institutional Review Board: Study 1: 1464P1CP-2, Study 2: 1464P3CP-5), and all individuals provided written informed consent to participate. All procedures were carried out in accordance with ethical principles of the Declaration of Helsinki and Good Clinical Practice.

2.1.1 | Study 1

Period 1 (Days 1–7) comprised the esaxerenone alone, single-dose administration phase of the study. A single esaxerenone 2.5 mg tablet (Daiichi Sankyo Co., Ltd., Tokyo, Japan) was administered orally on Day 1 (start of Period 1), in the fasting state (fasting for ≥10 h before and 4 h after administration; Figure 1), after which subjects rested in a sitting position for 4 hours. The esaxerenone tablet was administered with 200 mL water; no other beverage consumption was permitted for 1 hour before or 2 hours after study drug administration. Caffeinated drinks were prohibited during the hospitalisation period, and the only food permitted was prepared by the study centre and provided at predetermined times.

Period 2 (Days 8–17) comprised the coadministration phase of the study, commencing 7 days after the first dose of esaxerenone. On Day 8, 200-mg oral itraconazole tablets (ITRIZOLE Capsules 50; Janssen Pharmaceutical KK, Tokyo, Japan) were administered twice daily with 200 mL of water: 1 dose 30 minutes after breakfast and another 30 minutes after dinner. Breakfast and dinner consisted of 500–600 kcal of total energy, of which fat accounted for 20–30%, and each meal was consumed within 20 minutes. On Days 9–16, a 200–mg itraconazole tablet was administered once daily 30 minutes after breakfast. On Day 13, a single 2.5-mg dose of esaxerenone was administered with a 200-mg itraconazole tablet in the fasting state as previously described (Figure 1). A final follow-up visit occurred on Days 29–31.

2.1.2 | Study 2

A similar 2-period study design was implemented for Study 2, with an esaxerenone single dose administered at the beginning of Period 1 (Days 1–7) and esaxerenone plus rifampicin coadministered during Period 2 (Days 8–17). In Period 1, esaxerenone 5 mg was administered orally on Day 1 (Figure 1), following the same food and beverage conditions as described for Study 1. During Period 2 (starting on Day 8), 600 mg rifampicin (RIFADIN Capsules; Daiichi Sankyo Co., Ltd., Tokyo, Japan) was administered orally with 200 mL of water once daily before breakfast for 9 days. On Day 13, a single oral dose of 5 mg esaxerenone was administered in a fasted state 2 hours after administration of 600 mg rifampicin (Figure 1). A final follow-up visit occurred on Days 29–31.

2.2 | Study population

Inclusion criteria for the 2 studies were identical: healthy Japanese males aged 20–45 years; body mass index (BMI) ≥18.5 kg m^{-2} and <25.0 kg m^{-2}; BP <140/90 mmHg; and heart rate ≤99 beats min^{-1}.

Key exclusion criteria for both studies were: a history of serious conditions, including central nervous system, cardiovascular, respiratory, blood, gastrointestinal, hepatic/renal, thyroid, pituitary gland or adrenal diseases; any drug hypersensitivity; drug or alcohol dependence; and a positive hepatitis B surface antigen, hepatitis C virus antibody, syphilis or HIV antibody test result. Subjects were also excluded if they had undergone whole blood collection of ≥1200 mL within 1 year, ≥400 mL within 84 days or ≥200 mL within 28 days before screening, or plasmapheresis or platelet apheresis within 14 days before screening. Exclusion criteria also comprised any symptom considered clinically significant by the investigator or subinvestigator, or any abnormal electrocardiograph finding at screening, or a deviation in laboratory data from the reference range of the study centre at screening. Drugs, food or supplements containing St John's Wort, concomitant therapies, the consumption of grapefruit (juice or pulp) within 7 days before admission, and any medical treatment from another physician since the screening examination, were prohibited.

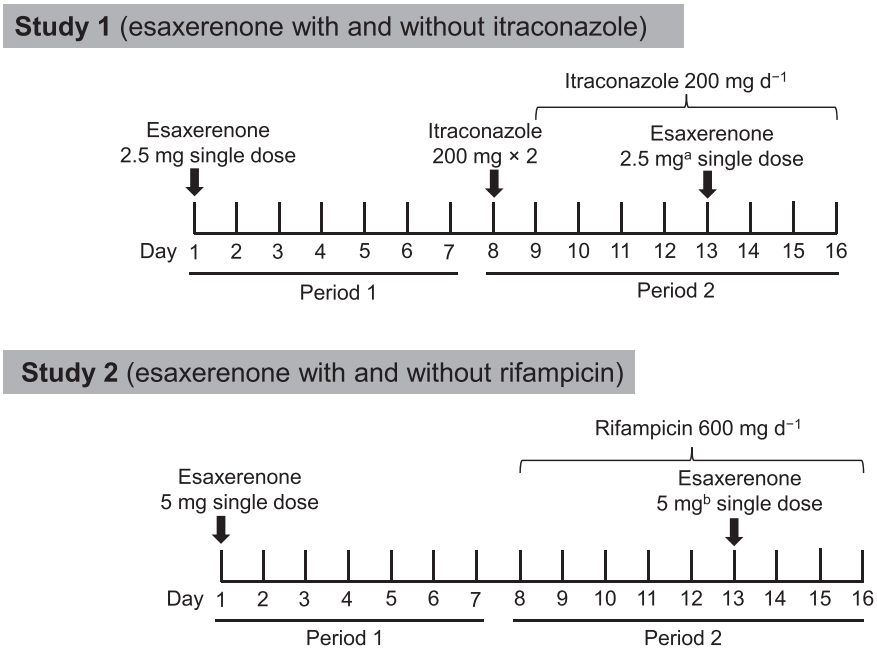

FIGURE 1 Study designs: [a]2.5 mg esaxerenone was administered in a fasting state concomitantly with itraconazole; [b]5 mg esaxerenone was administered in a fasting state 2 hours after rifampicin administration

2.3 | PK assessments

2.3.1 | Blood sampling for PK assays

In Study 1, blood samples (3 mL) were collected to measure the plasma concentrations of esaxerenone on Day 1 (Period 1) and Day 13 (Period 2). Samples were collected predose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, 36, 48, 60, 72 and 96 hours after esaxerenone administration.

In Study 2, blood samples (8 mL) were collected to measure plasma concentrations of esaxerenone and its metabolites on Day 1 (Period 1) and Day 13 (Period 2). As in Study 1, samples were collected predose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, 36, 48, 72 and 96 hours after esaxerenone administration.

Plasma for assays of esaxerenone and its metabolites was obtained by centrifugation (1700 *g* for 10 minutes at 4°C) and was frozen (−20°C or lower) until the assays were performed.

2.3.2 | Plasma assay

Plasma samples were treated by solid phase extraction (Oasis HLB μElution Plate; Waters Corporation, Milford, MA, USA), and drug concentrations were measured by liquid chromatography–tandem mass spectrometry.

2.3.3 | Esaxerenone and its oxidised metabolite (M1)

The methodology for chromatographic separation and determination for esaxerenone has been reported previously.[3,4] Multiple-reaction monitoring of the esaxerenone metabolite M1 (m/z 421 to 224) and its internal standard (d3-M1, m/z 424 to 24) were conducted. For M1 test samples of 0.3, 4.0 and 80.0 ng mL^{-1}, intrastudy assay precisions were 2.2, 3.2 and 2.6%, respectively; the assay accuracy ranged from −2.8 to 6.3% (lower limit of quantification [LLOQ] 0.1 ng mL^{-1}).

2.3.4 | Esaxerenone metabolites: M4 and M11

Chromatographic separation was performed using a CAPCELL PAK C18 MGII column (Shiseido Co., Ltd.; Tokyo, Japan) with an internal diameter of 2.0 mm, length of 150 mm and pore size of 3 μm. Detection was performed using an API 5000 tandem mass spectrometer with TurboIonSpray source by electrospray ionisation in the negative ion mode; multiple-reaction monitoring of M4 (m/z 641 to 447), M11 (m/z 488 to 312) and their internal standard (d7-esaxerenone, m/z 472 to 370) was conducted. For M4 test samples of 0.1, 0.3, 4.0 and 80.0 ng mL^{-1}, intrastudy assay precisions were 2.9–6.3, 4.8–7.1, 1.0–6.5 and 2.5–6.6%, respectively; the assay accuracy ranged from −3.9 to 8.0% (LLOQ 0.1 ng mL^{-1}). For M11 test samples of 0.1, 0.3, 4.0 and 80.0 ng mL^{-1}, intrastudy assay precisions were 3.8–6.7, 2.4–4.6, 1.6–4.1 and 2.3–7.6%, respectively; the assay accuracy ranged from −13.5 to 5.0% (LLOQ 0.1 ng mL^{-1}).

2.3.5 | PK analysis

PK parameters were calculated using noncompartmental analysis, using Phoenix WinNonlin (version 6.3; Certara, Princeton, NJ, USA). For Studies 1 and 2, the primary endpoints were maximum plasma concentration (C_{max}), area under the plasma concentration–time curve (AUC) to the last quantifiable time (AUC_{last}) and AUC from time zero to infinity (AUC_{inf}) for esaxerenone. Secondary endpoints in both

studies included time to maximum esaxerenone concentration (t_{max}), esaxerenone half-life ($t_{1/2}$) and apparent total body clearance (CL/F). Study 2 also assessed C_{max}, AUC_{last} and AUC_{inf} for esaxerenone metabolites, and ratios of plasma metabolites to parent (esaxerenone; M/P) for C_{max}, AUC_{last} and AUC_{inf}, which were adjusted to accommodate differences in molecular weight between esaxerenone and its metabolites.

2.4 | Safety and tolerability

Safety was evaluated through the assessment of adverse events (AEs), laboratory tests, vital signs (BP, pulse rate and body temperature) and 12-lead electrocardiogram. AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA/J versions 19.0 and 19.1) System Organ Class and Preferred Terms.

2.5 | Sample size

The sample sizes for both studies were calculated assuming within-subject variations in C_{max} and AUC of 20 and 10%, respectively, based on a previous study.[4]

For Study 1, assuming that geometric least-squares mean (GLSM) ratios of C_{max} and AUC were ≤1.05, when ratios were estimated after a single oral dose of esaxerenone and concomitant itraconazole administration, a sample size of 18 subjects would provide ≥80% statistical power with 2-sided 90% confidence intervals (CIs) for GLSM ratios of C_{max} and AUC to detect the CIs within 0.80–1.25. To allow for unexpected circumstances, such as subject withdrawals, the number of subjects was specified as 20.

For Study 2, it was estimated that 12 subjects would be required. Two-sided 90% CIs of GLSM ratios of C_{max} and AUC, when ratios were estimated after a single oral dose of esaxerenone and concomitant rifampicin administration, were assumed to be 0.2–1.0 based on a case series of 12 subjects (unpublished data on file, Daiichi Sankyo Co., Ltd.). The estimation accuracy for GLSM ratios was within about 10% in all cases, indicating sufficient accuracy for assessing DDIs.

2.6 | Statistical analyses

In all studies, the PK analysis sets included subjects who received esaxerenone, and for whom data were available for at least 1 primary endpoint in Periods 1 and 2. The safety analysis sets included all subjects who agreed to participate in the study and who received at least 1 dose of esaxerenone, itraconazole or rifampicin. Differences between the results when esaxerenone was administered alone or with itraconazole or rifampicin, were calculated using GLSM ratios and their 90% CIs. If the GLSM ratio was contained within the bounds (0.80–1.25) of the 90% CIs, it was inferred that there was no DDI. For all statistical analyses, SAS software (version 9.2; SAS Institute, Cary, NC, USA) was used.

2.7 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY.

3 | RESULTS

3.1 | Baseline characteristics

A total of 20 subjects were enrolled in, and completed, Study 1. The mean (standard deviation [SD]) age was 29.9 (6.91) years, height was 172 (5.99) cm and BMI was 21.4 (1.69) kg m^{-2} (Table 1).

A total of 12 subjects were enrolled in Study 2; 1 subject was withdrawn because of an AE (rash) and was not included in the analysis. The mean (SD) age was 31.9 (8.12) years, height was 169 (6.48) cm and BMI was 22.3 (1.31) kg m^{-2} (Table 1).

3.2 | Effects of itraconazole on esaxerenone PK (Study 1)

The plasma concentration–time profile for esaxerenone is shown in Figure 2a. A slight increase in C_{max} was observed when esaxerenone was coadministered with itraconazole (mean [SD], 41.7 [8.46] ng mL^{-1}) compared with esaxerenone alone (36.7 [5.36] ng mL^{-1}). However, mean values for AUC_{last} and AUC_{inf} were approximately 50% greater with coadministration *vs* esaxerenone alone (AUC_{last} 920 [186] *vs* 625 [113] ng h mL^{-1}; AUC_{inf} 996 [219] *vs* 648 [121] ng h mL^{-1}). The median (range) t_{max} of esaxerenone when coadministered with itraconazole and when administered alone were 2.00 (1.00–4.00) hours and 2.25 (1.50–4.00) hours, respectively. The mean $t_{1/2}$ for esaxerenone was slightly prolonged after coadministration with itraconazole (25.9 [4.21] h) compared with esaxerenone alone (20.7 [3.96] h; Table 2).

The GLSM ratio (90% CI) of the C_{max} with and without coadministration of itraconazole was 1.13 (1.05, 1.20), which was within the *no-DDI* range of 0.80 to 1.25. However, GLSM ratios (90%

TABLE 1 Demographic characteristics of subjects at baseline (pharmacokinetic analysis set)

Characteristics	Study 1 (*n* = 20)	Study 2 (*n* = 11[a])
Age, y	29.9 (6.91)	31.9 (8.12)
Height, cm	172 (5.99)	169 (6.48)
Weight, kg	63.0 (5.88)	64.1 (6.87)
Body mass index, kg m^{-2}	21.4 (1.69)	22.3 (1.31)

Values are mean (standard deviation).
[a]One subject was withdrawn due to an adverse event and not included in this analysis.

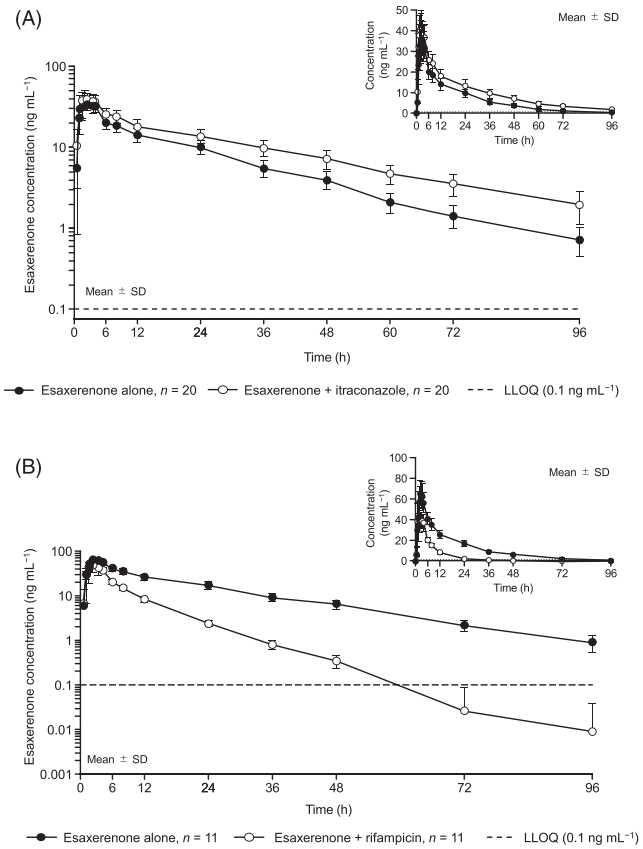

FIGURE 2 Plasma concentration–time profiles for esaxerenone, administered alone and in combination with (A) itraconazole or (B) rifampicin (semi-log plots; insets show linear plots). LLOQ, lower limit of quantification; SD, standard deviation

CI) of AUC_{last} and AUC_{inf} were 1.47 (1.40–1.54) and 1.53 (1.45–1.62), respectively, and were, therefore, above the no-DDI range (Table 2).

3.3 | Effects of rifampicin on esaxerenone PK (Study 2)

Exposure to esaxerenone decreased in the presence of rifampicin (Figure 2b; Table 3). The mean C_{max} decreased by 34.1% when esaxerenone was coadministered with rifampicin (47.6 [6.22] ng mL^{-1}) rather than administered alone (72.4 [10.1] ng mL^{-1}), and the AUC_{last} and AUC_{inf} were approximately 70% lower with coadministration *vs* esaxerenone alone (AUC_{last} 347 [24.5] *vs* 1110 [149] ng h mL^{-1}; AUC_{inf} 351 [24.8] *vs* 1130 [150] ng h mL^{-1}). The median (range) t_{max} of esaxerenone when coadministered with rifampicin or administered alone were 2.50 (1.00–4.00) hours and 2.50 (1.50–3.50) hours, respectively. The mean $t_{1/2}$ for esaxerenone was markedly shortened after coadministration with rifampicin (8.63 [1.67] h) compared with esaxerenone alone (16.6 [2.38] h; Table 3).

Esaxerenone C_{max}, AUC_{last} and AUC_{inf} GLSM ratios (90% CI) when coadministered with rifampicin, compared with esaxerenone alone, were 0.659 (0.599–0.724), 0.315 (0.300–0.332) and 0.312 (0.297–0.328), respectively, and were below the no-DDI range of 0.80–1.25 (Table 3).

3.4 | Effects of rifampicin on esaxerenone metabolites (Study 2)

Exposure to esaxerenone metabolites in the presence of rifampicin is shown in Figures 3a–c, and the PK parameters are listed in Table 4.

TABLE 2 Pharmacokinetic parameters for esaxerenone alone and in combination with itraconazole

	Esaxerenone 2.5 mg		Ratio[a] (90% CI)
	Alone (*n* = 20)	+ Itraconazole (*n* = 20)	
Arithmetic mean values[b]			
C_{max}, ng mL^{-1}	36.7 (5.36)	41.7 (8.46)	–
AUC_{last}, ng h mL^{-1}	625 (113)	920 (186)	–
AUC_{inf}, ng h mL^{-1}	648 (121)	996 (219)	–
t_{max}, h	2.25 (1.50–4.00)	2.00 (1.00–4.00)	–
$t_{1/2}$, h	20.7 (3.96)	25.9 (4.21)	–
CL/F, L h^{-1}	3.98 (0.696)	2.61 (0.477)	–
GLSM values			
C_{max}, ng mL^{-1}	36.4	41.0	1.13 (1.05, 1.20)
AUC_{last}, ng h mL^{-1}	616	904	1.47 (1.40, 1.54)
AUC_{inf}, ng h mL^{-1}	637	976	1.53 (1.45, 1.62)

[a](Esaxerenone + itraconazole)/(esaxerenone alone).
[b]Values are mean (standard deviation) or median (range) for t_{max}.
AUC_{inf}, area under the plasma concentration–time curve up to infinity; AUC_{last}, area under the concentration–time curve up to the last quantifiable time; CI, confidence interval; CL/F, apparent total body clearance; C_{max}, maximum plasma concentration; GLSM, geometric least-squares mean; $t_{1/2}$, terminal elimination half-life; t_{max}, time to reach C_{max}.

TABLE 3 Pharmacokinetic parameters for esaxerenone alone and in combination with rifampicin

	Esaxerenone 5 mg		
	Alone (*n* = 11)	+ rifampicin (*n* = 11)	Ratio[a] (90% CI)
Arithmetic mean values[b]			
C_{max}, ng mL^{-1}	72.4 (10.1)	47.6 (6.22)	–
AUC_{last}, ng h mL^{-1}	1110 (149)	347 (24.5)	–
AUC_{inf}, ng h mL^{-1}	1130 (150)	351 (24.8)	–
t_{max}, h	2.50 (1.50–3.50)	2.50 (1.00–4.00)	–
$t_{1/2}$, h	16.6 (2.38)	8.63 (1.67)	–
CL/F, L h^{-1}	4.50 (0.634)	14.3 (1.01)	–
GLSM values			
C_{max}, ng mL^{-1}	71.7	47.2	0.659 (0.599, 0.724)
AUC_{last}, ng h mL^{-1}	1098	346	0.315 (0.300, 0.332)
AUC_{inf}, ng h mL^{-1}	1121	350	0.312 (0.297, 0.328)

[a](Esaxerenone + rifampicin)/(esaxerenone alone).
[b]Values are mean (standard deviation) or median (range) for t_{max}.
AUC_{inf}, area under the plasma concentration–time curve up to infinity; AUC_{last}, area under the concentration–time curve up to the last quantifiable time; CI, confidence interval; CL/F, apparent total body clearance; C_{max}, maximum plasma concentration; GLSM, geometric least-squares mean; $t_{1/2}$, terminal elimination half-life; t_{max}, time to reach C_{max}.

For M1, C_{max} and AUC_{last} were increased (more than doubled) by coadministration of rifampicin (Table 4). The M/P ratios for C_{max} and AUC_{last} for M1 were increased after coadministration of esaxerenone and rifampicin compared with esaxerenone alone (Table 4). The $t_{1/2}$ and AUC_{inf} of M1 could not be estimated because of the lack of an apparent terminal phase owing to a long $t_{1/2}$ for M1.

The C_{max} for M4 did not differ markedly after administration of esaxerenone plus rifampicin, compared with esaxerenone alone, whereas AUC_{last} and AUC_{inf} decreased by approximately 40% when esaxerenone was coadministered with rifampicin. The $t_{1/2}$ for M4 decreased from 17.3 (2.34) to 7.72 (3.12) hours in the presence of rifampicin. M/P ratios for C_{max}, AUC_{last} and AUC_{inf} for M4 were increased by coadministration of rifampicin compared with esaxerenone alone (Table 4).

The C_{max} of M11 decreased by approximately 50%, and AUC_{last} and AUC_{inf} were reduced by approximately 20% when esaxerenone was coadministered with rifampicin; $t_{1/2}$ decreased from 17.4 (2.53) to 7.14 (0.783) hours. M/P ratios for C_{max}, AUC_{last} and AUC_{inf} for M11 were decreased for esaxerenone coadministered with rifampicin *vs* esaxerenone alone (Table 4).

3.5 | Safety

No serious AEs occurred in either study. Treatment-emergent AEs (TEAEs) were reported by 1 subject in Study 1 and 2 subjects in Study 2 (Table 5). In Study 1, the only TEAE was increased blood creatine phosphokinase level, which occurred after the first dose of esaxerenone (mild severity; resolved without treatment) and was not considered by the investigator to be causally related to treatment. In Study 2, TEAEs considered by the investigator to be related to treatment were rash with esaxerenone alone (moderate severity; resolved with treatment) and increased eosinophil level (mild severity; resolved without treatment). Early withdrawal due to a TEAE occurred in 1 subject who experienced rash in Study 2. No clinically meaningful abnormalities in vital signs, electrocardiogram parameters or other laboratory values were observed in either study.

4 | DISCUSSION

These 2 studies clinically evaluated the effects of a strong CYP3A inhibitor, itraconazole, and a strong CYP3A inducer, rifampicin, on esaxerenone PK.

In Study 1, coadministration of itraconazole increased mean esaxerenone C_{max}, AUC_{last} and AUC_{inf} by 12.6, 46.8 and 53.1%, respectively, and slightly prolonged the mean $t_{1/2}$ for esaxerenone. The slight increase in esaxerenone C_{max} observed after coadministration with itraconazole is likely due to increased esaxerenone bioavailability, which, in turn, may be secondary to increased absorption of esaxerenone caused by the inhibition of intestinal P-gp and inhibition of the CYP3A involved in first-pass metabolism in the small intestine and liver. The contribution of CYP3A to esaxerenone clearance was considered to be about 1/3 in the previously published mass-balance study,[5] and there was sufficient plasma exposure of itraconazole to esaxerenone during the esaxerenone PK assessment period in the current study. Hence, our observed 1.5-fold increase in esaxerenone AUCs during coadministration with itraconazole was considered a reasonable change, given that the 1/3 of esaxerenone clearance due to CYP3A was almost completely inhibited by itraconazole, reducing overall esaxerenone clearance to the remaining 2/3. Thus, the increase in esaxerenone exposure with itraconazole coadministration in the current study appears to be because of reduced esaxerenone clearance. However, the slightly

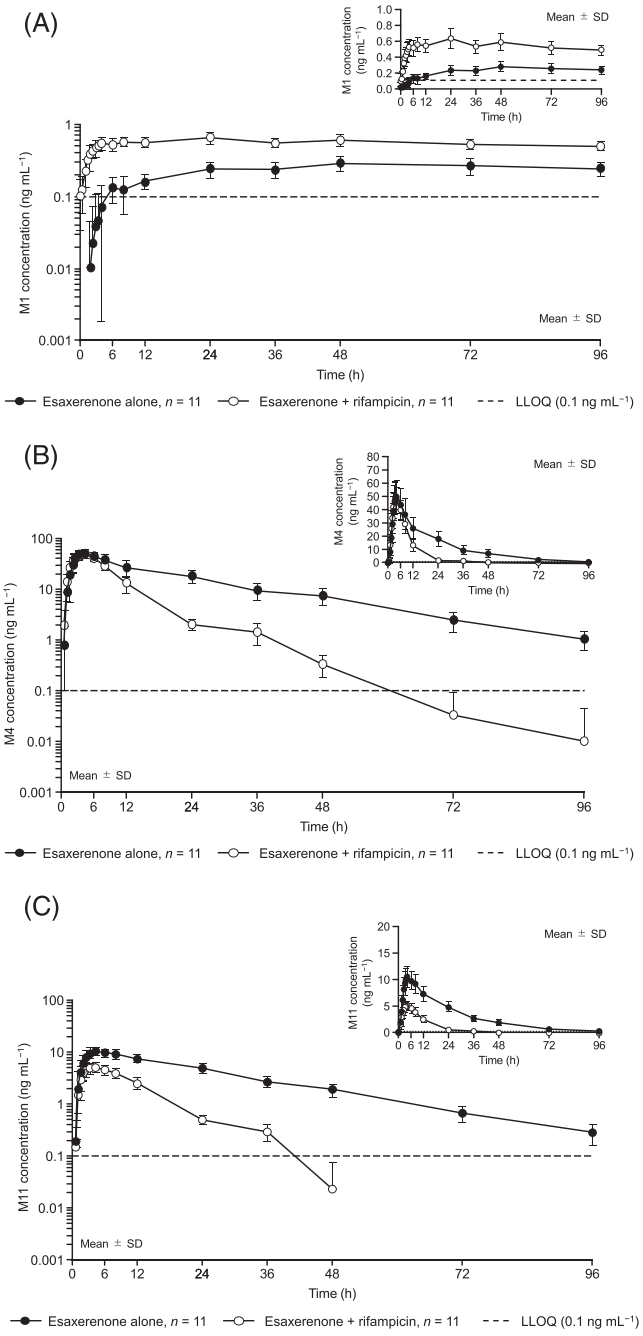

FIGURE 3 Plasma concentration–time profiles for: (A) M1, esaxerenone oxidised metabolite (semi-log plot; inset shows linear plot); (B) M4, *O*-glucuronide (semi-log plot; inset shows linear plot); and (C) M11, acyl-glucuronide of amide-bond hydrolysate (semi-log plot; inset shows linear plot), when esaxerenone was administered alone or in combination with rifampicin. LLOQ, lower limit of quantification; SD, standard deviation

increased esaxerenone AUC we observed was less pronounced than a corresponding 5-fold increase in eplerenone exposure in the presence of ketoconazole.[6] Although the 1.5-fold increase in esaxerenone AUC caused by itraconazole is unlikely to be of major clinical significance, this clinical interaction should not be overlooked in future therapeutic settings. Because it is generally known that serum K^+ elevation is a side effect of MR antagonists, clinicians should exercise caution when treating patients with concurrent strong CYP3A inhibitors and esaxerenone.

In Study 2, exposure to esaxerenone decreased in the presence of rifampicin. That is, coadministration with rifampicin decreased mean esaxerenone C_{max}, AUC_{last} and AUC_{inf} by 34.1, 68.5 and 68.8%, respectively, compared with administration of esaxerenone alone. Esaxerenone CL/F increased and its $t_{1/2}$ was shortened when coadministered with rifampicin. Regarding the CYP3A induction effect of rifampicin, the dosing regimen of rifampicin in this study (600 mg once daily) was specifically selected to achieve a maximum induction effect of CYP3A, as previously described.[9]

It has been suggested that esaxerenone has multiple metabolic pathways: oxidation, glucuronidation and hydrolysis.[5] Therefore, we evaluated the effects of rifampicin coadministration on the disposition of esaxerenone metabolites M1, M4 and M11, which were formed by CYP3A, UGT or hydrolysis followed by glucuronidation, respectively. Because of the long $t_{1/2}$ for M1, we cannot rule out the possibility that there may have been some carry-over effect from Period 1 on the plasma concentration of M1 in Period 2. However, the data suggest that the increased plasma concentration of M1 in Period 2 was probably caused by CYP3A induction by rifampicin (Figure 3A).

M4 is formed by several UGT isoforms (1A1, 1A3, 1A9, 2B7 and 2B15),[5] and the M/P ratio for M4 based on C_{max}, AUC_{last} and AUC_{inf} was increased when esaxerenone was coadministered with rifampicin, suggesting increased clearance of esaxerenone derived from induction of UGTs by rifampicin.

The M/P ratio for M11, based on C_{max}, AUC_{last} and AUC_{inf}, was reduced when esaxerenone was coadministered with rifampicin. Induction of both CYP3A and UGTs by rifampicin may have reduced the contribution of hydrolysis to total metabolism, resulting in an M/P ratio decrease for M11.

Overall, the observed changes in exposure of esaxerenone and its metabolites in the presence of rifampicin suggest that rifampicin induction of both CYP3A and UGTs explains the overall decrease in exposure to unchanged esaxerenone. The decreased esaxerenone C_{max} was probably because of decreased bioavailability resulting from increased intestinal and hepatic first-pass metabolism, secondary to induction of CYP3A and UGTs by rifampicin. Additionally, reduced esaxerenone bioavailability may also be attributed to the induction of intestinal P-gp by rifampicin, leading to reduced esaxerenone absorption. Therefore, esaxerenone efficacy may be reduced when the drug is administered concomitantly with rifampicin.

In both studies, esaxerenone was safe and well tolerated when administered concomitantly with either itraconazole or rifampicin. However, as previously noted, it may be clinically prudent to monitor serum K^+ levels when esaxerenone is coadministered with strong CYP3A inhibitors.

Ethnic differences in the frequency of polymorphisms of CYP3A have been reported; however, they have rarely been linked to differences in PK between ethnic groups.[10] In a study assessing PK differences of esaxerenone in Japanese and Caucasian subjects, mean esaxerenone plasma concentrations after the administration

TABLE 4 Pharmacokinetic parameters for esaxerenone metabolites following administration of a single dose of esaxerenone and in combination with rifampicin

Parameter[a]	Esaxerenone 5 mg		Metabolite/parent ratio	
	Alone (*n* = 11)	+ rifampicin (*n* = 11)	Alone (*n* = 11)	+ rifampicin (*n* = 11)
M1 (oxidised metabolite)				
C_{max}, ng mL^{-1}	0.281 (0.065)	0.652 (0.123)	0.004 (0.001)	0.015 (0.003)
AUC_{last}, ng h mL^{-1}	21.5 (5.24)	51.4 (8.05)	0.021 (0.003)	0.163 (0.021)
AUC_{inf}, ng h mL^{-1}	NA	NA	NA	NA
t_{max}, h	48.0 (48.0–72.0)	23.9 (3.50–47.8)	–	–
$t_{1/2}$, h	NA	NA	–	–
M4 (*O*-glucuronide)				
C_{max}, ng mL^{-1}	50.7 (12.5)	49.4 (8.54)	0.510 (0.101)	0.760 (0.131)
AUC_{last}, ng h mL^{-1}	1080 (326)	453 (94.5)	0.710 (0.199)	0.947 (0.185)
AUC_{inf}, ng h mL^{-1}	1100 (332)	455 (94.8)	0.713 (0.200)	0.943 (0.183)
t_{max}, h	4.00 (3.00–4.00)	4.00 (2.50–4.00)	–	–
$t_{1/2}$, h	17.3 (2.34)	7.72 (3.12)	–	–
M11 (acyl-glucuronide of amide-bond hydrolysate)				
C_{max}, ng mL^{-1}	10.7 (1.95)	5.25 (0.802)	0.141 (0.013)	0.106 (0.016)
AUC_{last}, ng h mL^{-1}	278 (49.3)	63.5 (11.8)	0.241 (0.038)	0.174 (0.029)
AUC_{inf}, ng h mL^{-1}	286 (50.9)	66.3 (11.9)	0.242 (0.038)	0.180 (0.028)
t_{max}, h	4.00 (3.00–6.00)	3.50 (3.00–4.00)	–	–
$t_{1/2}$, h	17.4 (2.53)	7.14 (0.783)	–	–

[a]Values are arithmetic mean (standard deviation) or median (range) for t_{max}.
AUC_{inf}, area under the plasma concentration–time curve up to infinity; AUC_{last}, area under the concentration–time curve up to the last quantifiable time; CL/F, apparent total body clearance; C_{max}, maximum plasma concentration; NA, not assessable because the elimination rate constant (K_{el}) is not appropriately estimated; $t_{1/2}$, terminal elimination half-life; t_{max}, time to reach C_{max}.

TABLE 5 Treatment-emergent adverse events (safety analysis set)

Adverse events	Study 1		Study 2	
	Esaxerenone 2.5 mg		Esaxerenone 5 mg	
	Alone (*n* = 20)	+ Itraconazole (*n* = 20)	Alone (*n* = 12)	+ Rifampicin (*n* = 11[a])
Rash	0	0	1 (8.3)	0
Eosinophil count increased	0	0	0	1 (9.1)
Blood creatine phosphokinase increased	1 (5.0)	0	0	0

Value is the number of subjects, and percentages were calculated using the number of subjects in the column heading as the denominator.
[a]One subject was withdrawn due to an adverse event and not included in this analysis.

of esaxerenone 20 mg were similar for both ethnicities (unpublished data on file, Daiichi Sankyo Co., Ltd.). Based on these results, it is unlikely that differences in CYP3A expression between Japanese and Caucasian populations influence esaxerenone metabolism.

Limitations of our study included intersubject heterogeneity in CYP3A activity and the potential for CYP3A modulation by concomitant medications. In addition, the long elimination half-life of M1 may have confounded the interpretation of the M/P results. In patients in a relevant clinical setting, the wider context of overall efficacy and safety should be considered when determining the clinical relevance of the observed DDIs. In particular, the influence of strong CYP3A inhibitor-induced changes in esaxerenone exposure on overall esaxerenone safety warrant further evaluation.

In conclusion, itraconazole increased esaxerenone AUC_{inf} by 53.1%, and rifampicin decreased esaxerenone AUC_{inf} by 68.8%. Therefore, caution is advised when coadministering esaxerenone with strong inhibitors and inducers of CYP3A.

CLINICAL TRIAL REGISTRATION

Study 1 with itraconazole: JapicCTI-163286; Study 2 with rifampicin: JapicCTI-163443.

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COMPETING INTERESTS

Y.K., T.I., M.K., T.S., T.N., Y.N. and H.I. are employees of Daiichi Sankyo Co., Ltd. M.S., H.U. and S.I. have no potential conflicts of interest to disclose.

CONTRIBUTORS

T.N. and T.I. performed all statistical analyses and Y.K. drafted the manuscript. M.S., H.U. and S.I. conducted the study and collected the data. All authors contributed to the design and implementation of the research and provided critical feedback on the manuscript. All authors approved the final manuscript before submission.

DATA AVAILABILITY STATEMENT

All de-identified patient data relevant to this study are included in this article. Additional data and supporting documents pertaining to this study, such as the study protocol and statistical analysis plan, are provided upon reasonable request made via this web address (https://vivli.org/ourmember/daiichi-sankyo/) in accordance with the data sharing policy of Daiichi Sankyo Co., Ltd.

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