Effects of Food and Calcium Carbonate on the Pharmacokinetics of Lusutrombopag, a Novel Thrombopoietin Receptor Agonist

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ABSTRACT

Purpose: Lusutrombopag is a novel, orally active thrombopoietin receptor agonist. This report describes 3 studies aimed at assessing the effects of food and calcium carbonate on the pharmacokinetic parameters of lusutrombopag in healthy subjects.

Methods: Three single-dose, open-label crossover studies were conducted. In study 1, eighteen healthy subjects were administered a single 2-mg dose of lusutrombopag as a single tablet in the fasted or fed state or as a 2-mg solution in the fasted state. In study 2, fifteen healthy subjects were administered a single 0.75-mg dose of lusutrombopag as three 0.25-mg tablets in the fasted or fed state, or in the fasted state with coadministration of 4000-mg calcium carbonate. In study 3, fifteen healthy subjects were administered 4-mg lusutrombopag as a single tablet in the fasted or fed state. Pharmacokinetic parameters were estimated from plasma lusutrombopag concentrations.

Findings: Mean fed versus fasted state ratios (90% CIs) of C_{max} and $AUC_{0-\infty}$, respectively, were: 0.904 (0.864−0.945) and 0.920 (0.886−0.956) (study 1); 0.972 (0.864−1.09) and 1.02 (0.945−1.11) (study 2); and 0.917 (0.842−0.999) and 0.908 (0.855−0.964) (study 3). The respective ratios for calcium carbonate versus no calcium carbonate (fasted state) were 1.08 (0.959−1.21) and 0.989 (0.913−1.07) (study 2). Lusutrombopag exposure remained unaffected, except for a slight decrease in exposure with food. Lusutrombopag exposure did not change with the coadministration of calcium carbonate. These findings suggest that there was no clinically significant effect of food or calcium carbonate on the bioavailability of lusutrombopag. Each treatment regimen was well tolerated.

Implications: According to the present findings, no specific restrictions are required for lusutrombopag administration with regard to meals (including those with dairy products), mineral supplements, or coadministration of antacids. Clinical trial registration: JapicCTI-No.: JapicCTI-194690, JapicCTI-194689. ClinicalTrials.gov identifier: NCT03897413. (*Clin Ther*. 2019;41:1747−1754)

Keywords: calcium, food effect, lusutrombopag, pharmacokinetics, thrombopoietin receptor agonist.

INTRODUCTION

Lusutrombopag (also known as S-888711) is a small-molecule, orally active thrombopoietin receptor agonist (TPO-RA) discovered and developed by Shionogi & Co, Ltd (Osaka, Japan).[1] Lusutrombopag acts on the transmembrane domain of human TPO receptors expressed in megakaryocytes; it stimulates megakaryocyte proliferation and differentiation via the same signal transduction system as that of endogenous TPO and promotes thrombocytopoiesis.

Thrombocytopenia is a common complication of chronic liver disease (CLD). Patients with CLD and severe thrombocytopenia (platelet count <50,000/μL)[2] are at greater risk of bleeding during invasive medical

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procedures as well as during the postprocedure period. Patients with CLD and thrombocytopenia may therefore benefit from access to approved pharmacotherapeutic options that can help increase their platelet count before undergoing planned invasive procedures. Currently, lusutrombopag is approved and commercially available for this indication in Japan, the United States, and the European Union.

Lusutrombopag was shown to have linear pharmacokinetic profile in the range of doses tested (0.25−50 mg). The T_{max} of lusutrombopag was ~4 h, and the $t_{1/2}$ was ~20 h. The primary elimination pathway of lusutrombopag was via fecal excretion, and plasma concentrations of lusutrombopag metabolites (deshexyl and 5-keto) were notably lower than those of unchanged lusutrombopag. Furthermore, the concentration-dependent thrombopoiesis induced by lusutrombopag was reported in a population pharmacokinetic/pharmacodynamic analysis.[3] Because potential drug−food interactions may affect the pharmacokinetic profile of lusutrombopag and could inadvertently reduce or increase its pharmacologic effect, it is important to evaluate the effect of food on the pharmacokinetic profile of lusutrombopag.

Exposure to eltrombopag, another small-molecule TPO-RA, was significantly decreased with a high-fat and high-calcium meal.[4] This decrease in exposure may be attributed to chelation of polyvalent cations such as calcium, magnesium, and iron. The molecular structure of lusutrombopag does not suggest a potential for chelation of polyvalent cations; however, the *in vivo* effect of polyvalent cations on the pharmacokinetic profile of lusutrombopag was evaluated. Calcium carbonate is used as an antacid[5]; thus, the effect of coadministration of antacids on the pharmacokinetic profile of lusutrombopag should also be evaluated. The current article describes 3 studies assessing the effect of food and calcium carbonate on the pharmacokinetic profile of lusutrombopag in healthy subjects, with the purpose of identifying any potential restrictions regarding meal intake, dairy products, mineral supplements, and coadministration of antacids.

SUBJECTS AND METHODS

Study Design

Three single-dose, open-label, 3-period crossover studies were conducted. Healthy adult subjects were enrolled and randomized to the treatment regimens in a crossover cohort.

Study 1 (study number 0801M0612; JapicCTI-194690) was a 3-period crossover study aimed to evaluate the relative bioavailability and effect of a high-fat meal on the pharmacokinetic profile of lusutrombopag. The study included subjects in fed and fasted states who were given a single dose of lusutrombopag as a 2-mg tablet. In addition, subjects received a single administration of lusutrombopag as a 10-mg tablet in the fed state to evaluate the pharmacokinetic parameters of lusutrombopag. Eighteen healthy adult male subjects were enrolled in the crossover group, and 8 healthy adult male subjects were enrolled in the 10-mg dose group; all enrolled subjects completed the study. Lusutrombopag 2 mg was administered as a solution (~20 mL) that was prepared in the morning, immediately before use, and administered in the fasted state; as a 2-mg tablet in the morning in the fasted state; as a 2-mg tablet in the morning in the fed state; and as a 10-mg tablet in the morning in the fed state.

Study 2 (study number 0924M0618; NCT03897413) was a 3-period crossover study aimed to evaluate the effect of a high-fat meal and calcium carbonate on the pharmacokinetic profile of lusutrombopag after a 0.75-mg dose administered as three 0.25-mg tablets. Fifteen healthy adult male and female subjects were enrolled, and 14 subjects completed the study. One subject in study 2 (fed state) was withdrawn after receiving lusutrombopag in the first period because of a personal reason but no drug-related event. Lusutrombopag 0.75 mg was administered as three 0.25-mg tablets in the morning in the fasted state; as three 0.25-mg tablets in the morning in the fed state; and as three 0.25-mg tablets with 4000 mg of calcium carbonate (1600 mg of calcium)[5] in the morning in the fasted state.

Study 3 (study number 1218M061A; JapicCTI-194689) was a 3-period crossover study aiming to evaluate the relative bioavailability of lusutrombopag (4-mg tablet vs 1-mg tablet) and the effect of a high-fat meal on the pharmacokinetic profile of lusutrombopag after administration of a 4-mg tablet. Fifteen healthy adult male subjects were enrolled and completed the study. Lusutrombopag 4 mg was administered as four 1-mg tablets in the morning in the fasted state; as a 4-mg tablet in the morning in

the fasted state; and as a 4-mg tablet in the morning in the fed state.

All 3 studies were conducted under the principles of Good Clinical Practice. The institutional review boards of CPC Clinic (Kagoshima, Japan) for study 1, IntegReview (Austin, Texas) for study 2, and Kyushu Clinical Pharmacology Research Clinic (Fukuoka, Japan) for study 3 approved implementation of the studies. Consent to this research was obtained directly from all the candidate subjects in a written form before initiation of any procedures in all 3 studies.

In all studies, blood samples for the quantification of lusutrombopag plasma concentrations were collected into tubes containing sodium heparin. The details of food, pharmacokinetic blood sampling time points, and washout interval are provided in Supplemental Table I (see the online version at https://doi.org/10.1016/j.clinthera.2019.06.004).

Bioanalytical Methods

Plasma samples for pharmacokinetic analysis underwent deproteinization by using acetonitrile. In the extract obtained by the deproteinization, lusutrombopag was assayed with a validated HPLC-MS/MS method by using the positive ion mode and multiple reaction monitoring. The calibration curve range was 1.00−2000 or 0.100−100 ng/mL. The precision and accuracy were 0.8%−12.7% and −9.6% to 14.7%, respectively, for the measurement. The lower limit of quantitation was 1 ng/mL for study 1 and 0.100 ng/mL for the other studies.

Pharmacokinetic Analysis

The following pharmacokinetic parameters were calculated based on the plasma concentrations of lusutrombopag according to noncompartmental analysis: C_{max}, T_{max}, AUC_{0-last}, $AUC_{0-\infty}$, and $t_{1/2}$. The pharmacokinetic parameters were calculated by using Phoenix WinNonlin version 5.0.1 or higher (Certara USA Inc, Princeton, New Jersey).

Statistical Analysis

An ANOVA was performed by using PROC MIXED with SAS version 9.1 or higher (SAS Institute, Inc, Cary, North Carolina), which included terms for treatment, sequence, and period as fixed effects and subject-within-sequence as a random effect for the ln-transformed values of pharmacokinetic parameters. ANOVA was performed separately for each study. The point estimates and 90% CIs were generated for the differences between treatments for ln-transformed pharmacokinetic parameters. The point estimates and 90% CIs were back-transformed to obtain the corresponding geometric least squares mean ratios (GMRs) and 90% CIs.

Safety Assessment

For each treatment, safety was monitored by physical examinations, vital sign measurements, 12-lead ECGs, clinical laboratory tests, and reporting of adverse events (AEs). The number of treatment-emergent AEs (TEAEs) was recorded.

RESULTS

Study Subjects

The baseline demographic and clinical characteristics of study subjects are given in Supplemental Table II (see the online version at https://doi.org/10.1016/j.clinthera.2019.06.004). The ranges of age were 20−34 years, 19−70 years, and 20−37 years in study 1 (crossover cohort), study 2, and study 3, respectively. All subjects were male in study 1 and study 3, and 8 of 15 subjects were female in study 2. The ranges of body mass index were 18.6−24.8 kg/m^2, 20.6−29.7 kg/m^2, and 19.8−24.9 kg/m^2 in study 1 (crossover cohort), study 2, and study 3.

Pharmacokinetic Parameters

Table I displays the pharmacokinetic parameters of lusutrombopag for each treatment. The results of the statistical analysis of the effect of food or calcium carbonate on the C_{max}, AUC_{0-last}, and $AUC_{0-\infty}$ of lusutrombopag are presented in Table II.

In study 1, the plasma concentration profiles of lusutrombopag after a single dose of lusutrombopag 2-mg solution in the fasted state and a 2-mg tablet in the fasted or fed state are shown in Fig. 1. The plasma concentration profiles were similar among the treatments. The GMRs (90% CIs) of C_{max}, AUC_{0-last}, and $AUC_{0-\infty}$ were 0.904 (0.864−0.945), 0.921 (0.887−0.956), and 0.920 (0.886−0.956), respectively, for fed versus fasted states among subjects receiving the 2-mg tablet. The exposure to lusutrombopag in the fed state was slightly lower

Table I. Pharmacokinetic parameters of lusutrombopag according to treatment regimen. Data in the table are shown as geometric mean (%CV for the geometric mean).

Study	Treatment	N	C_{max} (ng/mL)	T_{max}* (h)	AUC_{0-last} (ng · h/mL)	$AUC_{0-\infty}$ (ng · h/mL)	$t_{1/2}$ (h)
Study 1	2-mg solution (fasted)	18	105 (14.2)	4.0 (3.0, 10.0)	2630 (23.5)	2700 (22.9)	23.7 (17.5)
	2-mg tablet (fasted)	18	93.2 (13.5)	4.0 (4.0, 10.0)	2450 (21.6)	2510 (20.6)	23.4 (15.2)
	2-mg tablet (fed)	18	84.2 (10.7)	5.0 (4.0, 10.0)	2250 (20.8)	2310 (20.0)	23.2 (15.0)
	10-mg tablet (fed)	8	326 (17.1)	5.0 (4.0, 10.0)	9460 (19.6)	9610 (20.0)	24.1 (11.3)
Study 2	3 × 0.25-mg tablet (fasted)	14	19.2 (30.2)	5.0 (4.0, 6.0)	488 (26.0)	538 (26.1)	24.1 (7.9)
	3 × 0.25-mg tablet (fed)	14	18.5 (18.8)	6.0 (4.0, 12.0)	511 (18.5)	549 (18.8)	23.2 (15.6)
	3 × 0.25-mg tablet (fasted) with calcium carbonate	14	20.5 (29.0)	4.0 (4.0, 8.0)	505 (20.3)	528 (20.1)	23.1 (13.9)
Study 3	4 × 1-mg tablet (fasted)	15	179 (17.0)	4.0 (4.0, 10)	5124 (17.0)	5220 (17.4)	26.1 (11.6)
	4-mg tablet (fasted)	15	165 (20.3)	4.0 (4.0, 10)	4685 (20.9)	4776 (21.5)	27.0 (10.8)
	4-mg tablet (fed)	15	151 (18.7)	4.0 (3.0, 5.0)	4256 (22.1)	4336 (22.6)	26.5 (11.2)

* Median (range).

Table II. Statistical analysis for effects of food and calcium carbonate on pharmacokinetic parameters of lusutrombopag.

Effect	Study and Dose (Formulation)	Parameter	GMR	90% CI for GMR (Lower Limit, Upper Limit)
Effect of food	Study 1, 2 mg (2-mg tablet)	C_{max}	0.904	0.864, 0.945
		AUC_{0-last}	0.921	0.887, 0.956
		$AUC_{0-\infty}$	0.920	0.886, 0.956
	Study 2, 0.75 mg (3 × 0.25-mg tablet)	C_{max}	0.972	0.864, 1.09
		AUC_{0-last}	1.03	0.944, 1.13
		$AUC_{0-\infty}$	1.02	0.945, 1.11
	Study 3, 4 mg (4-mg tablet)	C_{max}	0.917	0.842, 0.999
		AUC_{0-last}	0.909	0.855, 0.965
		$AUC_{0-\infty}$	0.908	0.855, 0.964
Effect of calcium carbonate	Study 2, 0.75 mg (3 × 0.25-mg tablet)	C_{max}	1.08	0.959, 1.21
		AUC_{0-last}	1.02	0.929, 1.12
		$AUC_{0-\infty}$	0.989	0.913, 1.07

GMR = geometric least squares mean ratio.

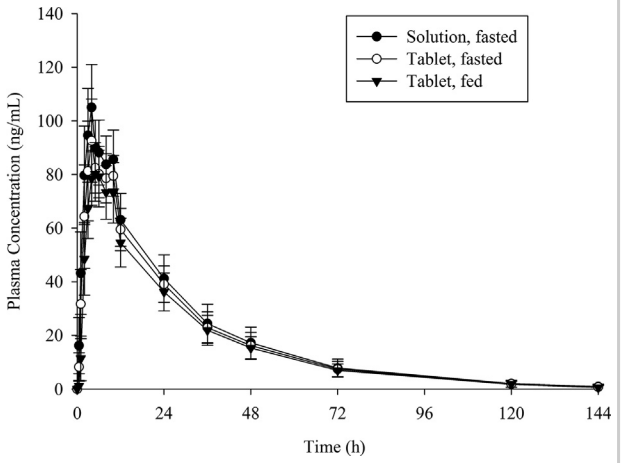

Figure 1. Mean plasma concentration profiles of lusutrombopag after a single 2-mg dose (2-mg tablet) in fasted and fed states and a 2-mg solution in fasted state. Values are given as mean (SD); 18 subjects per group.

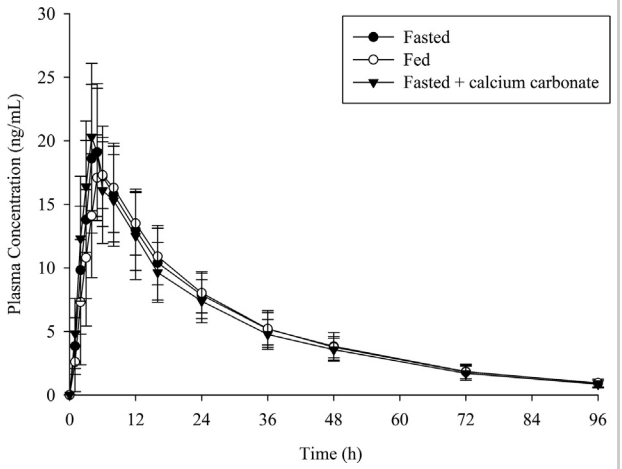

Figure 2. Mean plasma concentration profiles of lusutrombopag after a single 0.75-mg dose (three 0.25-mg tablets) in fasted and fed states and in fasted state with calcium carbonate. Values are given as mean (SD); fasted, 14 subjects; fed, 15 subjects; fasted with calcium carbonate, 15 subjects.

than that in the fasted state. The bioavailability of the tablet relative to the solution was 93% (see Supplemental Table III in the online version at https://doi.org/10.1016/j.clinthera.2019.06.004).

In study 2, the plasma concentration profiles of lusutrombopag after a single dose of lusutrombopag 0.75 mg administered as three 0.25-mg tablets in the fasted or fed state and coadministration with calcium carbonate in the fasted state are shown in Fig. 2. The plasma concentration profiles were similar among the treatments. The GMRs (90% CIs) of C_{max}, AUC_{0-last}, and $AUC_{0-\infty}$were 0.972 (0.864−1.09), 1.03 (0.944−1.13), and 1.02 (0.945−1.11), respectively, for fed versus fasted states; and 1.08 (0.959−1.21), 1.02 (0.929−1.12), and 0.989 (0.913−1.07) with calcium carbonate versus no calcium carbonate (fasted state). These results indicate no change in the lusutrombopag pharmacokinetic parameters with food intake or coadministration of calcium carbonate.

In study 3, the plasma concentration profiles of lusutrombopag after a single dose of lusutrombopag 4 mg as four 1-mg tablets in the fasted state and as a 4-mg tablet in the fasted or fed state are shown in Fig. 3. The plasma concentration profiles were similar among the treatments. The GMRs (90% CIs) of C_{max}, AUC_{0-last}, and $AUC_{0-\infty}$ were 0.917 (0.842−0.999), 0.909 (0.855−0.965), and 0.908 (0.855−0.964), respectively, for fed versus fasted states among subjects receiving the 4-mg tablet. The exposure to lusutrombopag in the fed state was slightly lower than that in the fasted state. The bioavailability of the 4-mg tablet relative to the 1-mg tablets was 92% (see Supplemental Table III in the online version at https://doi.org/10.1016/j.clinthera.2019.06.004).

Safety

No deaths, serious AEs, or AEs leading to discontinuation occurred in any of the 3 studies. In addition, no abnormal ECG findings or abnormal changes in vital signs were reported.

In study 1, two TEAEs (an increase in white blood cell count and an increase in neutrophil percentage) were reported in 1 subject who received the 2-mg lusutrombopag solution in the fasted state. One TEAE (skin laceration) was reported in 1 subject who received the 2-mg tablet in the fasted state, and 2

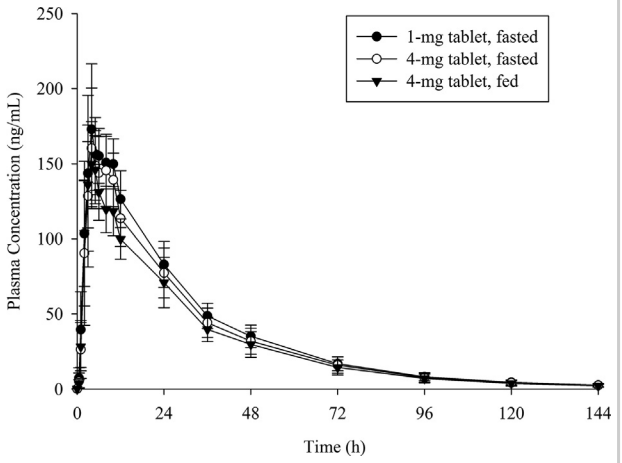

Figure 3. Mean plasma concentration profiles of lusutrombopag after a single 4-mg dose (4-mg tablet) in fasted and fed states and a single 1-mg dose (1-mg tablet) in fasted state. Values are given as mean (SD); 15 subjects per group.

TEAEs (an increase in white blood cell count and an increase in neutrophil percentage) were reported in 1 subject administered the 2-mg tablet in the fed state. Of these events, 4 TEAEs, in 2 of 18 subjects, were identified as adverse drug reactions (ADRs). Two ADRs were reported in 1 subject who received the 2-mg solution in the fasted state; and 2 ADRs were reported in 1 subject administered the 2-mg tablet in the fed state. The skin laceration was judged as moderate in severity because it required treatment; however, all other TEAEs were asymptomatic changes in laboratory values that were judged as mild in severity.

In study 2, four of the 15 subjects experienced at least 1 TEAE during the study. TEAEs reported for the treatment with calcium carbonate included headache (2 events), nausea (2 events), diarrhea (1 event), and contact dermatitis (1 event). One case of constipation in the fasted state treatment group (without coadministration of calcium carbonate) was identified as a TEAE. One subject experienced a TEAE while undergoing both treatments (with and without calcium carbonate) in the fasted state. Two subjects who received lusutrombopag with calcium carbonate reported headaches that were considered moderate in severity. All other TEAEs reported during the study were considered mild. None of the AEs reported were considered to be related to the study drug. All of the AEs reported were resolved.

In study 3, only 1 case of an increase in alanine aminotransferase level was reported as a TEAE in 1 of 15 subjects. The alanine aminotransferase level increased to 69 IU/L. This increase was considered mild in severity, and the event was asymptomatic. The alanine aminotransferase level was within the normal range 8 days after onset without any treatment. This TEAE was not considered related to the study drug. The C_{max} and $AUC_{0-\infty}$ of lusutrombopag in the subject who had the increased alanine aminotransferase levels for the 3 treatments (144−172 ng/mL and 3881−4218 ng h/mL, respectively) were not higher than the geometric means of C_{max} and $AUC_{0-\infty}$.

DISCUSSION

No clinically significant effect of food was observed on the bioavailability of lusutrombopag for any of the treatment regimens. The solubilization of lipophilic drugs is enhanced with fat or fat-induced bile secretion in the presence of a high-fat meal.[6] Lusutrombopag has poor water solubility; however, the solubility of lusutrombopag was significantly improved by the addition of a surfactant in the manufacturing process of the tablet formulation. This improved water solubility of lusutrombopag did not seem to affect the bioavailability of the drug in the presence of food.

Both solutions and tablet formulations were used for oral administration during the clinical development of lusutrombopag. The solutions were used in the initial Phase I studies in which doses of 0.1−50 mg were administered to evaluate the pharmacokinetic profiles and tolerability of lusutrombopag in healthy subjects. The 0.25- and 2-mg tablets were primarily used in the early-stage clinical studies to allow flexibility for dose selection and avoidance of excessive platelet increases. The 1-mg tablet was required to evaluate lusutrombopag doses of 2, 3, and 4 mg in the Phase IIb dose-finding study.[7] The composition was designed to be similar among these 3 tablets. The 3-mg tablet (commercial tablet) and 4-mg tablet were developed to improve stability of the tablets used in the early-stage clinical studies.

The different doses (0.75, 2, and 4 mg) were used in the 3 studies because each dose was selected as a clinical dose at the time of the study during the drug development. The 0.75-mg dose, which was lower than the approved dose (3-mg dose), was selected based on data from healthy subjects before conducting clinical studies for the target patients. Dose-normalized AUC in patients with CLD and severe thrombocytopenia suggested a dose-proportional exposure to lusutrombopag and a linear pharmacokinetic profile using different doses and tablets, including a 3-mg commercial tablet.[8] It was suggested that the results obtained in these clinical studies can be extrapolated to the 3-mg commercial tablet.

The commercially available formulation of lusutrombopag is the 3-mg tablet. In 1 of the 3 studies reported herein, we assessed the effect of food on the 4-mg tablet because at the time of the study, it was not known whether the 3- or 4-mg tablet would be commercialized for clinical use. The commercially available 3-mg tablet and the 4-mg tablet used in study 3 were designed to have a proportionally similar composition. Furthermore, it was confirmed in an *in vitro* analysis that the 3- and 4-mg tablets have comparable dissolution profiles. Given the linear pharmacokinetic profile of lusutrombopag,[3] it has been concluded that there is no influence of food on the bioavailability of the lusutrombopag 3-mg tablet. Consequently, restriction of food intake with the administration of the 3-mg tablet does not seem necessary. In the pivotal studies of lusutrombopag[9,10] in which lusutrombopag was administered as a 3-mg tablet without restriction of food intake, lusutrombopag exhibited efficacy and safety in the treatment of thrombocytopenia in patients with CLD undergoing invasive procedures.

The present results indicate that the coadministration of lusutrombopag with calcium carbonate had no effect on the pharmacokinetics of lusutrombopag, suggesting the absence of a pharmacokinetic interaction with polyvalent cations such as calcium, magnesium, and iron that are present in dairy products, mineral supplements, and antacids. The present results are consistent with the finding that the molecular structure of lusutrombopag cannot chelate polyvalent cations such as calcium, magnesium, and iron. Some drugs, including the antibiotic tetracycline, can form complexes with polyvalent cations, which prevents absorption.[6] Furthermore, exposure to eltrombopag, another TPO-RA, was decreased by 65% (C_{max}) and 59% ($AUC_{0-\infty}$) after the ingestion of a high-fat and high-calcium meal. Thus, eltrombopag seems to chelate polyvalent cations, such as calcium, magnesium, and iron, which may affect the pharmacokinetic profile of eltrombopag.[4] Moreover, calcium carbonate is known to alter the pH in the gastrointestinal tract.[5] However, such alterations of the pH did not seem to affect the bioavailability of lusutrombopag.

In the 3 studies reported herein, all AEs were mild or moderate. No severe AEs or discontinuations due to AEs were reported. All AEs were resolved during the study period. Overall, the present findings confirm that lusutrombopag was safe and well tolerated in all of the treatment regimens.

CONCLUSIONS

No specific restrictions are required for lusutrombopag administration with regard to meals (including those containing dairy products), mineral supplements, or coadministration of antacids. Lusutrombopag was safe and well tolerated among all groups of healthy subjects in this study.

CONFLICTS OF INTEREST

The authors are employees of Shionogi & Co, Ltd, which sponsored this research. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

The sponsor was involved in the study design, collection/analysis/interpretation of data, writing of the report, or the decision to submit the article for publication.

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Dr. Katsube analyzed the data and wrote the manuscript. Dr. Wajima reviewed the analyses and the manuscript. Mr. Fukuhara organized the clinical studies and reviewed the manuscript. Mr. Kano organized the clinical studies and reviewed the manuscript.

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SUPPLEMENTAL MATERIAL

Supplemental Table I. Food, pharmacokinetic sampling time points, and washout interval

Study	Food	Pharmacokinetic sampling time points	Washout interval
Study 1	Breakfast with total energy of 901 kcal (protein, 116 kcal; fat, 318 kcal; and carbohydrate, 467 kcal)	Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 72, 120, and 144 h, and in the 10-mg group, only at 288 h post dose	12 days between each administration
Study 2	Breakfast with total energy of approximately 1050 kcal (protein, 120 kcal; fat, 530 kcal; and carbohydrate, 400 kcal)	Pre-dose, 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 72, and 96 h post-dose	5 days between each administration
Study 3	Breakfast with a total energy content of 900 kcal (protein, 150 kcal; fat, 500 kcal; and carbohydrate, 250 kcal)	Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, and 144 h post-dose	12 days between each administration

Supplemental Table II. Baseline demographic and clinical characteristics of study subjects

Variable	Study 1 (crossover cohort)	Study 1 (10-mg dose cohort)	Study 2	Study 3
Number of subjects	18	8	15	15
Age (years)[a]	25.2 (20, 34)	22.4 (21, 26)	33.5 (19, 70)	25.7 (20, 37)
Sex				
Male	18	8	7	15
Female	0	0	8	0
Ethnicity				
Asian	18	8	2	15
Black or African American	0	0	1	0
Native Hawaiian or Other Pacific Islander	0	0	1	0
White	0	0	13	0
Weight (kg)[a]	62.10 (53.1, 70.7)	66.15 (59.2, 74.5)	74.11 (57.7, 93.6)	68.43 (60.5, 79.8)
Body mass index (kg/m^2)[a]	21.27 (18.6, 24.8)	22.19 (19.2, 24.4)	26.33 (20.6, 29.7)	22.83 (19.8, 24.9)

[a] Mean (range).

Supplemental Table III. Statistical analysis for comparisons of pharmacokinetic parameters of lusutrombopag between formulations in the fasted state

Study and formulation	Parameter	GMR	90% CI for GMR (lower limit, upper limit)
Study 1, 2-mg tablet versus solution	C_{max}	0.890	0.851, 0.931
	$AUC_{0\text{-last}}$	0.929	0.894, 0.964
	$AUC_{0\text{-inf}}$	0.931	0.896, 0.967
Study 3, 4-mg tablet versus 4 × 1-mg tablets	C_{max}	0.920	0.845, 1.002
	$AUC_{0\text{-last}}$	0.914	0.861, 0.971
	$AUC_{0\text{-inf}}$	0.915	0.862, 0.972

GMR, geometric least squares mean ratio; CI, confidence interval; C_{max}, maximum plasma concentration; $AUC_{0\text{-last}}$, area under the plasma concentration–time curve from time zero to the time of last quantifiable concentration after dosing; $AUC_{0\text{-inf}}$, area under the plasma concentration–time curve extrapolated from time zero to infinity.