

A Drug-Drug Interaction Study to Evaluate the Effect of TAS-303 on CYP3A Activity in the Small Intestine and Liver

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Yuji Kumagai, MD, PhD¹, Tomoe Fujita, MD, PhD^{1*}, Mika Maeda, BSc¹, Yoshinobu Sasaki, BSc¹, Makoto Nagaoka, MSc², Jinhong Huang, MD, PhD², Toru Takenaka, PhD², and Masaki Kawai, MSc² 

Abstract

TAS-303 (4-piperidinyl 2,2-diphenyl-2-[propoxy-1,1,2,2,3,3,3-*d*₇] acetate hydrochloride) is a novel selective noradrenaline reuptake inhibitor being developed for the treatment of stress urinary incontinence. An *in vitro* study and a physiologically based pharmacokinetic model simulation showed that TAS-303 had inhibitory potential against cytochrome P450 (CYP) 3A. This open-label, single-group study investigated the effect of TAS-303 on CYP3A activity by evaluating the pharmacokinetics (PK) of single-dose oral simvastatin 5 mg or intravenous midazolam 1 mg after repeated oral administration of TAS-303 3 mg in 12 healthy participants. TAS-303 plus simvastatin resulted in a 1.326-fold and a 1.420-fold increase of simvastatin in peak plasma concentration and area under the plasma concentration-time curve from time zero to time *t*, where *t* is the final time of detection (AUC_{0-t}), respectively. The addition of midazolam resulted in a 1.090-fold increase in the midazolam AUC_{0-t}. TAS-303 had a weak PK interaction with simvastatin but no apparent interaction with midazolam. TAS-303 at 3 mg/day is a weak inhibitor of intestinal but not hepatic CYP3A activity. No clinically important safety concerns related to TAS-303 were raised.

Keywords

drug-drug interactions, PBPK, clinical pharmacology, clinical trials (CTRs), pharmaceutical R & D (PRD), model & simulation

Stress urinary incontinence (SUI) is involuntary loss of urine on effort or physical exertion including sporting activities or on sneezing or coughing.^{1,2} This condition considerably compromises the quality of life for many women.^{3,4} TAS-303 (4-piperidinyl 2,2-diphenyl-2-[propoxy-1,1,2,2,3,3,3-*d*₇] acetate hydrochloride; Supplemental Figure S1) is a selective noradrenaline reuptake inhibitor that is being investigated as a novel therapy for SUI.⁵ In nonclinical studies, TAS-303 had a time-dependent inhibitory effect on cytochrome P450 (CYP) 3A, half-maximal inactivation (K_i , 1024 ng/mL), and a maximal inactivation rate constant (K_{inact} , 4.68 h⁻¹); unpublished data.

As many patients with SUI have complications that are associated with lifestyle diseases^{6,7} and are often elderly,^{8,9} they tend to use concomitant medications.¹⁰ CYP3A is present in both the small intestine and the liver and accounts for about 82% and 40% of total CYP activity, respectively.¹¹ In addition, CYP3A metabolizes approximately half of marketed drugs.¹² Therefore, clinical drug-drug interaction (DDI) studies of TAS-303 are needed to investigate any interaction with other drugs metabolized by CYP3A. We designed the present study to investigate the effects of TAS-303 on CYP3A in both the small intestine and the liver.

Draft guidance about clinical DDI studies from the US Food and Drug Administration¹³ stipulates that

simvastatin and midazolam are appropriate CYP3A substrates for use in DDI studies during drug development. These substrates are readily affected by drug interactions via inhibition or induction of CYP3A. Thus, the effects of TAS-303 on intestinal and hepatic CYP3A can be investigated using concurrent oral simvastatin that is metabolized by the intestinal and hepatic CYP3A, and the effects of TAS-303 on hepatic CYP3A can be investigated using intravenous midazolam that is metabolized by the hepatic CYP3A.

Before starting the present study, the predicted change in the area under the plasma concentration-time curve (AUC) ratio for simvastatin in the presence of

¹Kitasato University Hospital, Kanagawa, Japan

²Taiho Pharmaceutical Co., Ltd., Tokyo, Japan

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Corresponding Author:

Yuji Kumagai, MD, PhD 1-15-1, Kitasato, Minami-ku, Sagami-hara-city, Kanagawa, Japan

Email: kuma-guy@za2.so-net.ne.jp

*Present: Dokkyo Medical University, Tochigi, Japan

TAS-303 was estimated using a simulation: a physiologically based pharmacokinetic (PBPK) model.¹⁴⁻¹⁶ In the present study, intravenous midazolam was used as a test CYP3A substrate in addition to oral simvastatin because intrinsic hepatic clearance of simvastatin is high and its change caused by DDIs may not be accurately estimated.¹⁷⁻¹⁹

The objective of the present study was therefore to investigate the effects of TAS-303 on CYP3A activity in the small intestine and liver in healthy participants by evaluating the pharmacokinetics (PK) of single-dose oral simvastatin or intravenous midazolam, after repeated oral administration of TAS-303.

Methods

Study Design and Participants

This investigation was an open-label, single-group DDI study conducted at Kitasato University Hospital, Kanagawa, Japan, from October 13, 2015, until January 4, 2016. The study was conducted after review and approval by the institutional review board at the study site and after approval by the head of the study site. All participants provided written informed consent before participating in the study. The study was conducted in accordance with Good Clinical Practice and the ethical principles of the Declaration of Helsinki.

The study enrolled healthy Japanese men aged 20-40 years (at the time of providing written informed consent), with a body weight ≥ 50 kg and a body mass index (BMI) of 18.5-25.0 kg/m² (at screening). Subjects whose intake of any medication, supplement, grapefruit, or St. John's wort occurred within 7 days before starting simvastatin administration or of ethanol or caffeine occurred within 3 days before starting simvastatin administration were excluded.

Study Drug Administration

On day 1, simvastatin (LIPOVAS; MSD K.K., Tokyo, Japan) was administered as a single 5-mg oral dose (with 100-200 mL of water) after ≥ 10 hours of fasting (Figure 1). On day 3, 1 mg of midazolam (0.2 mL in a 2-mL vial; Midazolam Injection SANDOZ, Sandoz K.K., Tokyo, Japan) was administered intravenously for 1 minute. From day 4 (after a 24-hour washout period and after intravenous administration of midazolam) to day 21 except on day 19, 3 mg TAS-303 (12 \times 0.25-mg capsules) was administered with 150-250 mL of water, once daily (30 minutes after breakfast) for 18 days so that the interaction by TAS-303 can be maximized based on no clinically meaningful food effect on TAS-303 but approximately a 1.1-fold increase in AUC with meal in a preliminary food-effect assessment in a phase 1 study (data not shown). The dosage and administration of TAS-303 used in this study were set at 3 mg once daily, as this is the estimated maximum

dose and estimated dosage regimen for clinical use. On day 19 (at which plasma TAS-303 concentrations were presumably at steady state), single doses of 3 mg TAS-303 (12 \times 0.25-mg capsules) and 5 mg simvastatin were administered orally, with 150-250 mL of water, after ≥ 10 hours of fasting to reduce the inter- and intrasubject variability in simvastatin PK because simvastatin has highly variable PK. On day 21, 1 mg of midazolam was administered intravenously within 5 minutes of TAS-303 administration. Subjects were not permitted to intake any medication, supplement, grapefruit, St. John's wort, ethanol, or caffeine during this study.

Study Objectives

The key study objective was to investigate the effects of TAS-303 on CYP3A activity by evaluating the PK parameters peak plasma concentration (C_{max}), area under the plasma concentration-time curve from time zero to time t , where t is the final time of detection (AUC_{0-t}), and area under the plasma concentration-time curve from time zero to infinity (AUC_{0-inf}) for oral simvastatin (days 1 and 19) and for intravenous midazolam (days 3 and 21); point estimates for geometric mean (GM) ratios and 90% confidence intervals (CIs) in the TAS-303 + simvastatin/midazolam combination periods versus the simvastatin/midazolam monotherapy periods were calculated. The other objective was to assess the safety of TAS-303 when combined with midazolam and simvastatin, according to the occurrence of adverse events (AEs), adverse drug reactions, and physical findings in healthy Japanese participants.

Pharmacokinetic Assessments

For measurement of plasma simvastatin concentrations, a 3-mL blood sample was collected into a vacuum blood-sampling tube (treated with heparin sodium). Blood-sampling times were as follows. On days 1 and 19, blood samples were collected immediately before and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours after probe drug administration. For the measurement of plasma midazolam concentrations, a 2-mL blood sample was collected into a vacuum blood-sampling tube (treated with heparin sodium). Blood sampling times were as follows. On days 3 and 21, blood samples were collected immediately before and 0.083 (5 minutes), 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours after probe drug administration.

For the measurement of plasma TAS-303 concentrations, a 3-mL blood sample was sampled in a vacuum blood-sampling tube (treated with ethylenediaminetetraacetic acid dipotassium salt). Blood sampling times were as follows. On day 4 and days 15 to 18, blood samples were collected immediately before investigational product administration. On days 19 and 21, blood samples were collected immediately before and 1, 2,

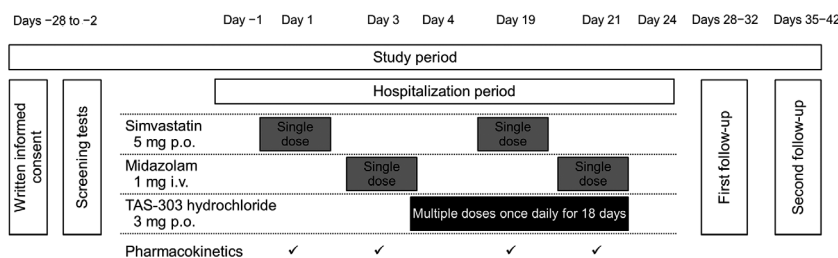


Figure 1. Study procedures. iv, intravenous; po, orally.

4, 6, 8, 12, and 24 hours after investigational product administration.

Plasma TAS-303 concentrations were measured by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. Plasma samples were spiked with stable isotope-labeled internal standard and were subjected to liquid-liquid extraction using dichloromethane. After the organic layer was evaporated under a stream of nitrogen gas, the residue was dissolved in 10 mmol/L ammonium acetate (pH 4.2)/methanol (70:30, v/v). The processed sample was injected into an LC-MS/MS system equipped with Capcell Pak C18 UG120 (2.0 mm i.d. × 150 mm; particle size, 5 μm; Shiseido Co., Ltd., Tokyo, Japan) as the analytical column, using methanol and 10 mmol/L ammonium acetate solution (pH 4.2) as the mobile phase. Electrospray ionization was performed in positive ion detection mode with a multiple reaction monitoring (MRM) mode on an API4000 (AB SCIEX, Framingham, Massachusetts). MRM transitions were m/z 361 to 294 for TAS-303 and m/z 364 to 304 for the internal standard. The range of quantification of TAS-303 was 0.2 to 200 ng/mL.

Plasma simvastatin concentrations were measured by validated LC-MS/MS method. Plasma samples were spiked with stable isotope-labeled internal standard and were subjected to solid-phase extraction. After the eluent was evaporated under a stream of nitrogen gas, the residue was dissolved in 1 mmol/L ammonium acetate (pH 4.5)/acetonitrile (50:50, v/v). The processed sample was injected into an LC-MS/MS system equipped with Ascentis Express C18 (2.1 mm i.d. × 150 mm; particle size, 2.7 μm; SUPELCO, Bellefonte, Pennsylvania) as the analytical column, using acetonitrile and 1 mmol/L ammonium acetate solution (pH 4.5) as the mobile phase. Electrospray ionization was performed in positive ion detection mode with an MRM mode on an API5000 (AB SCIEX). MRM transitions were m/z 419 to 285 for simvastatin and m/z 425 to 285 for the internal standard. The range of quantification of simvastatin was 0.05 to 50 ng/mL.

Plasma midazolam concentrations were measured by a validated LC-MS/MS method. Plasma samples were spiked with stable isotope-labeled internal standard and were subjected to solid-phase extraction.

The eluent was injected into an LC-MS/MS system equipped with InertSustain C18 HP (2.1 mm i.d. × 100 mm; particle size, 3 μm; GL Sciences Inc., Tokyo, Japan) as the analytical column, using methanol and 10 mmol/L ammonium acetate /0.1% acetic acid (50:50, v/v) as the mobile phase. Electrospray ionization was performed in positive ion detection mode with an MRM mode on a Triple Quad 6500 (AB SCIEX). MRM transitions were m/z 326 to 291 for simvastatin and m/z 330 to 295 for internal standard. The range of quantification of simvastatin was 0.05 to 100 ng/mL.

Statistical Analysis

The target sample size in this study was not statistically determined. A sample size of 12 participants was selected to allow for 2 dropouts and to constitute the PK evaluation ($n = 10$). The probability that the AUC_{0-inf} would meet the primary PK end-point criterion (90%CI for the GM ratio between the TAS-303 + simvastatin combination period and the simvastatin monotherapy period being within the range 0.80-1.25) was calculated by simulation and was found to be 0% in all simulations.

Model and Simulation

The PBPK modeling and simulation were conducted using a DDI simulator version 2.4 (Fujitsu Kyushu Systems Limited, Fukuoka, Japan), and the differential equations implemented have been reported previously.¹⁴

The input PK data for TAS-303 was K_I (1024 ng/mL), K_{inact} (4.68 h⁻¹), and the unbound fraction in the plasma (f_p , 0.025). They were obtained from in vitro studies of TAS-303 (unpublished data). The renal clearance value (0.64 L/h) was observed in a phase 1 single-dose study of TAS-303 (unpublished data). The fraction absorbed (F_a), intestinal availability (F_g), and blood-to-plasma concentration ratio were assumed to be 1.0. The liver-plasma concentration ratio was estimated within the DDI simulator using the calculated log partition coefficient (3.69) and f_p . TAS-303 plasma concentration-time profiles after a single oral administration were fitted into differential equations to obtain optimized values for intrinsic hepatic clearance ($CL_{h,int}$, 215 L/h), the absorption rate constant (0.198 h⁻¹), the volume of distribution

of the central compartment (277 L), the rate constant of transfer from the central compartment to the peripheral compartment (0.087 h^{-1}), and the rate constant of transfer from the peripheral compartment to the central compartment (0.099 h^{-1}) using Phoenix WinNonlin 6.4 (Certara L.P., Princeton, New Jersey). The degradation rate constants (K_{deg}) of CYP3A in the liver and intestine were $0.000321 \text{ min}^{-1}$ (elimination half-life [$t_{1/2}$], 36 hours) and 0.0005 min^{-1} ($t_{1/2}$, 23 hours), respectively.^{20,21} The values used for intestinal and hepatic blood flow and hepatic volume were default values in the DDI simulator version 2.4.

The input PK data for simvastatin were library values provided in the DDI simulator version 2.4, except for F_a and F_g values. Based on a 3.93-fold increase in the C_{max} of simvastatin that occurs when intestinal CYP3A is inhibited by grapefruit juice,^{22,23} the F_g of simvastatin was modified from 0.077 to 0.26. To compensate for the modification of F_g , the F_a of simvastatin was changed from 1.0 to 0.3. Simulations of a PK DDI between simvastatin and TAS-303 were conducted with the following 2 conditions: considering only inhibition in the liver and considering inhibition of both intestinal and hepatic metabolism. Simulations were based on multiple-dose administration of TAS-303, 3 mg once daily for 16 days, and administration of simvastatin 5 mg on day 14.

Descriptive statistics were used for baseline demographic and clinical characteristics, with n (%) for categorical variables and mean \pm standard deviation and median (range) for continuous variables. The safety analysis set comprised all participants who received at least 1 dose of TAS-303. The PK analysis set comprised all eligible participants who received the specified repeated administration of TAS-303 in combination with simvastatin or midazolam and who were evaluated for PK. The simvastatin analysis group comprised all eligible participants who received the specified repeated administration of TAS-303 from days 4 to 19, who received the specified single administration of simvastatin on days 1 and 19, and for whom the AUC or C_{max} of simvastatin on days 1 and 19 could be calculated. The midazolam analysis group comprised all eligible participants who received the specified repeated administration of TAS-303 from days 4 to 21, who received the specified intravenous administration of midazolam on days 3 and 21, and in whom the AUC or C_{max} of midazolam could be calculated.

PK parameters were calculated using Phoenix WinNonlin 6.4 (Certara L.P., Princeton, New Jersey). The following analyses were performed in the PK analysis set (simvastatin analysis group): GM ratios and 90% CIs for AUC_{0-t} , $\text{AUC}_{0-\text{inf}}$, C_{max} , $t_{1/2}$, apparent total clearance (CL/F), and apparent volume of distribution (V_d/F) for simvastatin in the TAS-303 + simvastatin

Table 1. Baseline Demographics and Clinical Characteristics (Safety Analysis Set)

	All Participants ^a (n = 12)
Men, n (%)	12 (100)
Japanese ethnicity, n (%)	12 (100)
Age, years	
Mean (SD)	29.0 (5.8)
Median (min, max)	27.0 (20, 39)
Height, cm	
Mean (SD)	170.9 (5.7)
Median (min, max)	170.5 (160.3, 180.0)
Weight, kg	
Mean (SD)	63.7 (5.4)
Median (min, max)	65.3 (53.6, 71.0)
Body mass index, kg/m ²	
Mean (SD)	21.8 (1.1)
Median (min, max)	21.9 (19.2, 23.1)
Medical history	
No	12 (100.0)
Yes	0 (0.0)
Active symptoms	
No	11 (91.7)
Yes	1 (8.3)

SD, standard deviation.

^aData for all 12 participants were the same for all 3 conditions (TAS-303 alone, + simvastatin, and + midazolam).

combination period versus the simvastatin monotherapy period. It was assumed that there were no PK interactions between TAS-303 and simvastatin if the 90%CI for the GM ratio fell within the range of 0.80-1.25. For the time to C_{max} (t_{max}) for simvastatin, the Wilcoxon signed rank test was performed for the TAS-303 + simvastatin combination period versus the simvastatin monotherapy period using EXSUS software version 8.0.0 (CAC Croit, Tokyo, Japan). In the PK analysis set (midazolam analysis group), for AUC_{0-t} , $\text{AUC}_{0-\text{inf}}$, initial plasma concentration (C_0), $t_{1/2}$, clearance (CL), and volume of distribution at steady state ($V_{d\text{ss}}$) of midazolam, 90% CIs for the GM ratios in the TAS-303 + midazolam combination period versus the midazolam monotherapy period were calculated.

To evaluate the safety of TAS-303 in the TAS-303 monotherapy period (days 4-19), TAS-303 + simvastatin combination period (days 19-21), and TAS-303 + midazolam combination period (days 21-24), the incidence of AEs and 2-sided 95% CIs were calculated. The proportion of participants who experienced an individual AE and 2-sided 95%CI were calculated. In addition, proportions were tabulated according to AE severity, whereas for adverse drug reactions, analyses were performed in the same way as for AEs.

Results

Participants

Twelve healthy Japanese participants were eligible for the study, received the study drug, and were included

Table 2. Simvastatin Pharmacokinetics When Administered Alone or in Combination With TAS-303

Parameter ^a	Arithmetic Mean (SD) ^b		Geometric Mean Ratio (90%CI) ^c
	Simvastatin Alone (Day 1)	Simvastatin + TAS-303 (Day 19)	
C_{max} , ng/mL	0.98 (0.47)	1.217 (0.4)	1.326 (1.089, 1.615)
t_{max} , h	1.00 (1.00, 3.00)	1.75 (1.00, 3.00)	NA
AUC_{0-t} , ng·h/mL	3.735 (3.166)	4.527 (1.730)	1.420 (1.041, 1.938)
AUC_{0-inf} , ng·h/mL	4.261 ^d (3.370)	4.878 (1.818)	1.333 (0.963, 1.845) ^d
$t_{1/2}$, h	2.6 (1.1) ^d	2.8 (0.7)	1.136 (0.932, 1.383) ^d
CL/F, L/h	1765.6 (1049.6) ^d	1196.1 (525.7)	0.750 (0.542, 1.039) ^d
V_d/F , L	5393 (1984) ^d	4452 (1262)	0.852 (0.687, 1.057) ^d

AUC_{0-t} , area under the plasma concentration-time curve from time zero to time t (where t is the final time of detection); AUC_{0-inf} , area under the plasma concentration-time curve from time zero to infinity; CI, confidence interval; CL/F, apparent total clearance; C_{max} , peak plasma concentration; NA, not applicable; t_{max} , time to C_{max} ; $t_{1/2}$, elimination half-life; V_d/F , apparent volume of distribution.

^aAll values are calculated for 12 participants, except when otherwise indicated.

^bValues are arithmetic mean (SD) for C_{max} , AUC_{0-t} , AUC_{0-inf} , $t_{1/2}$, CL/F, and V_d/F ; median (range) for t_{max} .

^cGeometric mean ratio for PK parameters for simvastatin + TAS-303 versus simvastatin alone.

^dEleven participants because the terminal phase for 1 participant was not observed.

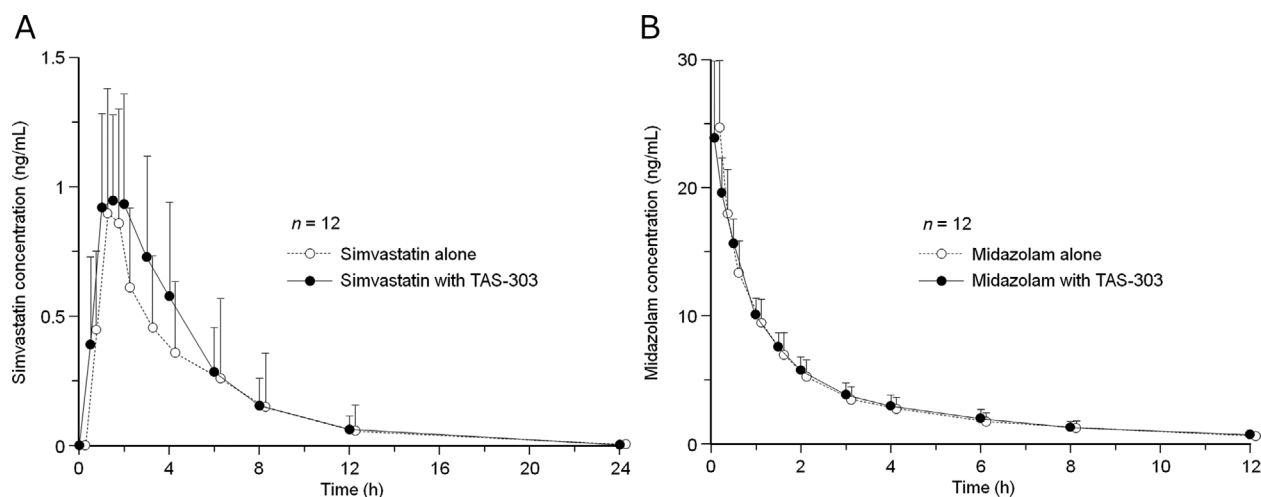


Figure 2. (A) Mean \pm SD plasma concentration-time profiles for simvastatin on day 1 (simvastatin alone) and day 19 (simvastatin + TAS-303) and (B) for midazolam on day 3 (midazolam alone) and day 21 (midazolam + TAS-303).

in the PK and safety analysis sets. All 12 participants were Japanese men with a median age of 27 years, (range, 20-39 years); see Table 1. Their median body weight was 65.3 kg (range, 53.6-71.0 kg), and the median BMI was 21.9 kg/m² (range, 19.2-23.1 kg/m²). None of the 12 participants had a previous medical history, although 1 participant had concurrent malocclusion. All 12 participants completed treatment with the study drug in the simvastatin monotherapy period (days 1-3), midazolam monotherapy period (days 3-4), TAS-303 monotherapy period (days 4-19), TAS-303 + simvastatin combination period (days 19-21), and TAS-303 + midazolam combination period (days 21-24).

Effect of TAS-303 on Simvastatin PK

After simvastatin alone on day 1, arithmetic mean \pm SD values for C_{max} , AUC_{0-t} , and AUC_{0-inf} were 0.980 \pm

0.471 ng/mL, 3.735 \pm 3.166 ng·h/mL, and 4.261 \pm 3.370 ng·h/mL, respectively (Table 2 and Figure 2A). Corresponding values on day 19 (ie, for simvastatin, after TAS-303 administration) were 1.207 \pm 0.336 ng/mL, 4.527 \pm 1.730 ng·h/mL, and 4.878 \pm 1.818 ng·h/mL (Table 2).

Point estimates (90%CI) for GM ratios for C_{max} , AUC_{0-t} , and AUC_{0-inf} were 1.326 (1.089-1.615), 1.420 (1.041-1.938), and 1.333 (0.963-1.845), respectively.

TAS-303 increased the simvastatin median t_{max} from 1.00 to 1.75 hours. There was no significant difference in this parameter ($P = .1641$, Wilcoxon signed rank test) between the simvastatin + TAS-303 period and the simvastatin monotherapy period. Point estimates (90%CI) for GM ratios for the $t_{1/2}$, CL/F, and V_d/F were 1.136 (0.932-1.383), 0.750 (0.542-1.039), and 0.852 (0.687-1.057), respectively (Table 2).

Table 3. Midazolam Pharmacokinetics When Administered Alone or in Combination With TAS-303

Parameter ^a	Arithmetic Mean (SD)		Geometric Mean Ratio (90%CI) ^b
	Midazolam Alone (Day 3)	Midazolam + TAS-303 (Day 21)	
C ₀ , ng/mL	29.2 (7.0)	30.7 (7.5) ^c	1.088 (0.935, 1.265) ^c
AUC _{0-t} , ng•h/mL	41.1 (9.0)	44.4 (7.2)	1.090 (1.030, 1.154)
AUC _{0-inf} , ng•h/mL	44.7 (11.0)	48.5 (8.79)	1.098 (1.035, 1.165)
t _{1/2} , h	3.7 (0.8)	3.9 (1.1)	1.056 (0.929, 1.200)
CL, L/h	23.7 (5.9)	21.3 (4.1)	0.911 (0.859, 0.966)
Vd _{ss} , L	85.95 (18.25)	81.77 (10.72)	0.964 (0.877, 1.061)

AUC_{0-t}, area under the plasma concentration-time curve from time zero to time t (where t is the final time of detection); AUC_{0-inf}, area under the plasma concentration-time curve from time zero to infinity; C₀, initial plasma concentration; CI, confidence interval; CL, clearance; t_{1/2}, elimination half-life; Vd_{ss}, volume of distribution at steady state.

^aAll values are calculated for 12 participants, except when otherwise indicated.

^bGeometric mean ratio for PK parameters for midazolam + TAS-303 versus midazolam alone.

^cNine participants because C₀ for 3 participants was not able to be estimated by back-extrapolation from the regression line for the first 2 data points with a positive slope.

Table 4. Incidence of Adverse Events According to Severity

Treatment	Event	Mild	Moderate	Severe	Total
Any treatment	Any event	10 (83.3)	2 (16.7)	0 (0.0)	12 (100.0)
TAS-303 + simvastatin	Paresthesia	1 (8.3)	0 (0.0)	0 (0.0)	1 (8.3)
	Diarrhea	1 (8.3)	0 (0.0)	0 (0.0)	1 (8.3)
TAS-303 + midazolam	Insomnia	1 (8.3)	0 (0.0)	0 (0.0)	1 (8.3)
	Somnolence	10 (83.3)	2 (16.7)	0 (0.0)	12 (100.0) ^a
TAS-303 alone	Back pain	1 (8.3)	0 (0.0)	0 (0.0)	1 (8.3)
	Alanine aminotransferase increased	1 (8.3)	0 (0.0)	0 (0.0)	1 (8.3)
Simvastatin alone	Headache	1 (8.3)	0 (0.0)	0 (0.0)	1 (8.3)
	Diarrhea	1 (8.3)	0 (0.0)	0 (0.0)	1 (8.3)
Midazolam alone	Monoparesis	1 (8.3)	0 (0.0)	0 (0.0)	1 (8.3)
	Somnolence	8 (66.7)	0 (0.0)	0 (0.0)	8 (66.7)
	Vertigo	1 (8.3)	0 (0.0)	0 (0.0)	1 (8.3)

Data are number of participants (%). There were no overlapping adverse events throughout any of the treatment periods.

^aThese were the only events for which a link to the study medication was considered "reasonably possible." All other adverse events were considered unrelated to the study medication.

Effect of TAS-303 on Midazolam PK

The relevant arithmetic mean \pm SD PK values for midazolam on days 3 and 21 are shown in Figure 2B and Table 3. The AUC_{0-t} was 41.10 \pm 9.03 and 44.37 \pm 7.15 ng•h/mL, respectively; CL was 23.68 \pm 5.87 and 21.31 \pm 4.14 L/h, respectively; and the Vd_{ss} was 85.95 \pm 18.25 and 81.77 \pm 10.72 L, respectively (Table 3). Point estimates (90%CI) for GM ratios for C₀, AUC_{0-t}, and AUC_{0-inf} were 1.088 (0.935-1.265), 1.090 (1.030-1.154), and 1.098 (1.035-1.165), respectively (Table 3).

Safety of TAS-303

No deaths or other serious AEs occurred, and no AEs leading to study discontinuation occurred in any participants. All AEs reported during the entire study resolved without treatment (Table 4). During combination therapy with TAS-303 and midazolam, somnolence was observed in 12 participants (mild in 10

participants and moderate in 2 participants). The investigator considered the cases to probably be attributable to midazolam, as midazolam is a hypnotic-sedative drug.²⁴ The investigator considered 1 case of monoparesis observed during the midazolam monotherapy period to be caused by blood sampling or the participant's condition.

Discussion

TAS-303 is a novel noradrenaline reuptake inhibitor that is being examined for its clinical capacity for the treatment of SUI. This PK study investigated the effects of TAS-303 on CYP3A activity and potential DDIs for TAS-303 in the small intestine and liver after single-dose oral simvastatin or intravenous midazolam in healthy Japanese participants. The present results show that 3 mg TAS-303 administered concomitantly with simvastatin has weak inhibitory potential against CYP3A in healthy participants and that any clinically

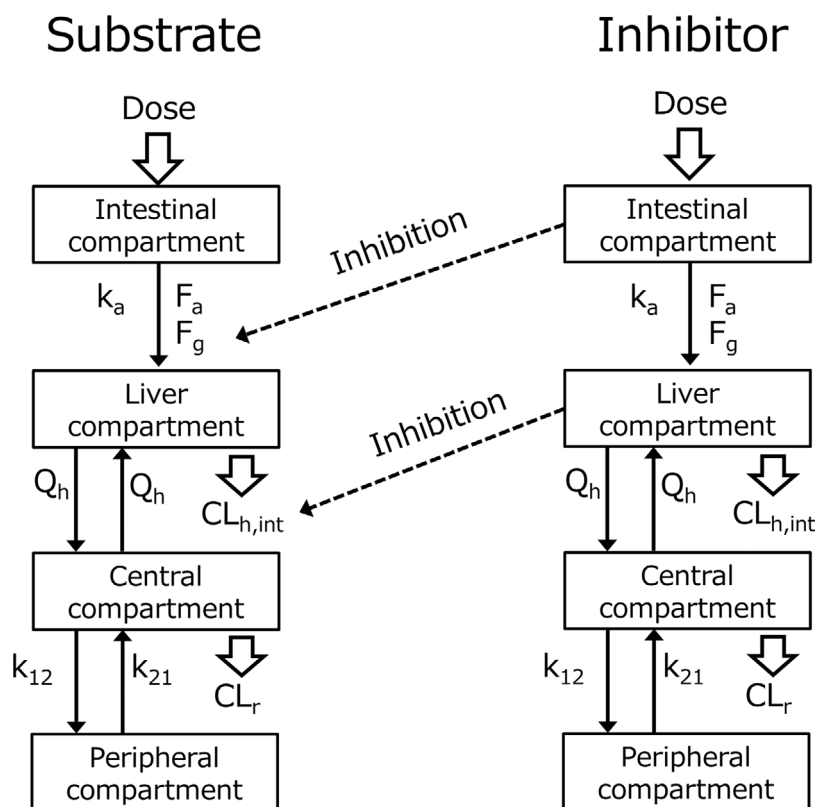


Figure 3. Structure of the PBPK model. $CL_{h,int}$, intrinsic hepatic clearance; CL_r , renal clearance; k_{12} , transfer rate constant from the central to the peripheral compartment; k_{21} , transfer rate constant from the peripheral to the central compartment; k_a , absorption rate constant; F_a , fraction absorbed; F_g , intestinal availability; Q_h , hepatic blood flow.

significant potential DDI between TAS-303 and midazolam is unlikely.

According to the guidelines from the Japanese Ministry of Health, Labor and Welfare²⁰ and draft guidance from the US Food and Drug Administration on drug interactions,¹³ 3 levels of DDI are defined, and, in general, PK interactions between 2 drugs are deemed absent if the 90%CI of the GM is between 0.8 and 1.25.

The 90%CIs of GM ratios (simvastatin plus TAS-303 versus simvastatin alone) for C_{max} , AUC_{0-t} , and AUC_{0-inf} for simvastatin indicated nonequivalence but weak CYP3A inhibition. This result suggests that the PK interaction between TAS-303 and simvastatin is weak.²⁰

The influence of TAS-303 on midazolam PK was evaluated using 90%CIs of GM ratios for AUC_{0-t} and AUC_{0-inf} . The 90%CIs of GM ratios (midazolam plus TAS-303 versus midazolam alone) for AUC_{0-t} and AUC_{0-inf} were within the range of 0.80-1.25. Therefore, TAS-303 is unlikely to have any clinically significant PK interaction with midazolam.

TAS-303 appeared to have no major clinical influence on midazolam, but TAS-303 had a weak effect on simvastatin (TAS-303 increased simvastatin C_{max} and AUC_{0-inf} by only about 30%). This effect suggests that

TAS-303 3 mg has a weak inhibitory effect on CYP3A only in the small intestine, but has no remarkable effect in the liver. This difference is probably because of differences in drug concentration between the small intestine and liver, that is, the hepatic concentration of TAS-303 3 mg probably did not reach a sufficient level to inhibit CYP3A in the liver. This result initially suggested that 3 mg of TAS-303 might increase plasma concentrations of orally administered CYP3A substrates via an inhibitory effect on first-pass intestinal metabolism mediated by CYP3A. However, 3 mg of TAS-303 has a minor inhibitory effect on first-pass hepatic metabolism and after CYP3A substrates reach the systemic circulation. Thus, there would be little effect of TAS-303 on $t_{1/2}$, and we would also anticipate no practical accumulation of CYP3A substrates. Indeed, in the present study, the actual GM ratio observed for $t_{1/2}$ (simvastatin plus TAS-303 versus simvastatin alone) was only 1.136.

In the present study, all participants were male, although most SUI patients are women. When this study ongoing, TAS-303 has not been finished the embryo-fetal development toxicity study. Therefore this study only included men. According to phase 1 studies of TAS-303 (unpublished data), there are no differences between men and women in the PK profile of TAS-303.

Therefore, the results of the present study can be applied to SUI patients. This PK profile provides helpful information for potential prescribers of TAS-303.

The AUC ratio of simvastatin in the presence of TAS-303, versus simvastatin alone was estimated before the study via a PBPK model (Figure 3) and was based on results from in vitro studies and phase 1 studies of TAS-303 (unpublished data). Based on the PBPK model, it was estimated that TAS-303 would increase the AUC of simvastatin 2.98-fold. This interaction was considered to occur primarily because TAS-303 inhibits CYP3A in the small intestine; hepatic CYP3A was not expected to be inhibited by TAS-303 (it was estimated from the increase in AUC_{0-t} in the PBPK model that TAS-303 would increase the AUC of simvastatin 1.09-fold when considering only TAS-303 inhibition of hepatic CYP3A). However, in the present study the actual AUC increase was 1.42-fold for simvastatin plus TAS-303, versus simvastatin alone. Thus, there is a marked discrepancy between the estimated and actual values for the AUC ratio. We suggest some possible reasons for this discrepancy: uncertainties in key input parameters, such as the K_{deg} of CYP3A, K_i , and K_{inact} of TAS-303, may be alienated from in vivo data; the differential equations for intestinal inhibition implemented in the DDI simulator provide a static rather than dynamic model, and not accounting for the intestinal tissue binding of TAS-303 in this model (the unbound fraction was assumed to be unity) may lead to an overestimation of unbound TAS-303 concentration in enterocytes and its inhibitory effect on intestinal CYP3A activity.^{25–28} To reasonably describe the observed DDI between TAS-303 and simvastatin, the current PBPK model of TAS-303 needs to be further refined based on emerging preclinical and clinical findings through the future development of TAS-303.

No AEs related to DDIs were observed in our study. Also, there were no clinically important safety concerns resulting from PK changes after 5 mg oral simvastatin or 1 mg intravenous midazolam plus 3 mg TAS-303 and caused by CYP3A inhibition.

Conclusions

The DDI between 3 mg TAS-303 and 5 mg simvastatin was weak and unlikely to be of clinical significance. Overall, TAS-303 3 mg per day is a weak inhibitor of CYP3A in the small intestine and is unlikely to have a significant effect on hepatic CYP3A activity. No clinical safety concerns were raised when 3 mg TAS-303 was administered in combination with 5 mg simvastatin or 1 mg midazolam, showing that oral TAS-303 can be safely administered concomitantly with intravenously administered CYP3A substrates.

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Conflicts of Interest

Yuji Kumagai has received consulting fees from Taiho Pharmaceutical Co., Ltd. Tomoe Fujita, Mika Maeda, and Yoshinobu Sasaki have no conflicts of interest to declare. All the remaining authors are employees of Taiho Pharmaceutical Co., Ltd. and own Otsuka Holdings Co., Ltd. stock.

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Data Sharing

Data will not be shared according to the sponsor policy on data sharing.

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Supplemental Information

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