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ORIGINAL RESEARCH ARTICLE

Pharmacokinetics, Pharmacodynamics and Population Pharmacokinetic/Pharmacodynamic Modelling of Bilastine, a Second-Generation Antihistamine, in Healthy Japanese Subjects

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Abstract

Background and objectives Bilastine is a novel second-generation antihistamine for the symptomatic treatment of allergic rhinitis and urticaria. The objective of this study was to evaluate the pharmacokinetics, pharmacodynamics, and tolerability of bilastine following single and multiple oral doses in healthy Japanese subjects. The pharmacokinetic and pharmacodynamic profiles were compared with those reported in Caucasian subjects.

Methods In a single-blind, randomized, placebo-controlled, parallel-group, single- and multiple-ascending dose study, bilastine tablets were administered at single doses of 10, 20, and 50 mg (Part I), and once daily for 14 days at 20 and 50 mg (Part II).

Results After single oral doses, maximum plasma concentrations (C_{max}) were reached at 1.0–1.5 h postdose. Plasma exposure [C_{max} and area under the plasma concentration-time curve (AUC)] increased dose-proportionally at single doses of 10–50 mg. In repeated-dose administration, no remarkable differences were observed between Day 1 and Day 14 for C_{max} or AUC. For inhibitory effects on wheal and flare response, bilastine 20 and 50 mg showed significant inhibition from 1.5 h after administration as compared with placebo, and the significant effect persisted for 24 h after administration. The rates of adverse events (AEs) were comparable between bilastine and placebo in both Part I and Part II. In addition, no dose- or administration period-dependent tendency of increase in rate of AEs or worsening of severity was observed.

Conclusion Bilastine exhibits similar single- and multiple-dose pharmacokinetic and pharmacodynamic characteristics in healthy Japanese subjects compared with those observed in Caucasian subjects in previous studies.

Key Points

Bilastine exhibited dose-proportional pharmacokinetics in Japanese subjects, and was well tolerated.

The pharmacokinetic and pharmacodynamic profiles in these Japanese subjects were similar to those of Caucasian subjects.

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1 Introduction

Bilastine, a novel second-generation H_1 antihistamine, has been granted marketing authorization for adults and adolescents (12 years and over) in most European countries

since 2010. The approved dose is 20 mg once a day for symptomatic treatment of allergic rhinoconjunctivitis and urticaria [1].

The pharmacokinetic (PK) profile of bilastine after single and multiple oral doses ranging from 5 to 220 mg has been reported in healthy Caucasian adult subjects. Absorption of bilastine is rapid and proportional to dose, with its oral bioavailability being reduced by foods and grapefruit juice [1]. Absolute oral bioavailability of bilastine is 60.67 % [2]. No accumulation pattern was shown for bilastine after repeated dosing in a 14-day PK study of escalating daily doses from 10 to 100 mg [3]. In the mass-balance study, bilastine was not significantly metabolized in humans and is largely eliminated unchanged both in urine (33.1 %) and feces (67 %) [4]. Population PK modeling with an indirect response model based on data from 310 healthy volunteers suggested that bilastine PK follows a two-compartmental model with first-order absorption and elimination [5].

Exposure and accumulation of bilastine are modified when the drug is simultaneously administered with some membrane transport protein inhibitors. In particular, bioavailability of bilastine is significantly increased when co-administered with P-glycoprotein (P-gp) inhibitors [1]. Bilastine is a substrate of P-gp and organic anion transporting polypeptide, but not of human breast cancer resistance protein, organic anion transporter 1 or 3, or organic cation transporter 2 [6]. Further, bilastine is not metabolized and does not interact significantly, either as an inhibitor or inducer, with the cytochrome P450 enzyme system, suggesting a low propensity for drug–drug interactions involving this metabolic pathway [7].

As part of the clinical development program in Japan to confirm extrapolation of foreign clinical data as support for new drug application in Japan, we conducted a phase I study to evaluate the PK, pharmacodynamics (PD), safety, and tolerability of bilastine in healthy Japanese subjects. The PK and PD results obtained in this study were subsequently compared with those previously reported for healthy Caucasian subjects.

2 Methods

This study was conducted in accordance with the ethical principles based on the Declaration of Helsinki, and Good Clinical Practice as defined by the Ministerial Ordinance concerning the standards for the implementation of clinical studies on pharmaceutical products, and the regulations stipulated in the Japanese Pharmaceutical Affairs Law. This study was conducted at Yanagibashi Hospital (Tokyo, Japan) in 2013. The protocol and the informed consent documents were approved by the institutional review board. All subjects gave written informed consent before the initiation of any study-specific procedure.

2.1 Study Design

This was a single-center, randomized, single-blind (for subjects), placebo-controlled, ascending dose, single and multiple dose study in 60 healthy male subjects to assess the PK, PD, safety, and tolerability of bilastine. The study consisted of two parts. In Part I, each subject received a single oral dose of bilastine [10, 20, or 50 mg (as 10 mg + 20 mg × 2 tablets)], or matching placebo ($n = 9$ active, $n = 3$/step placebo). Subjects ($n = 12$/step) were fasted overnight prior to dosing and remained fasted until 4 h postdose. In Part II, each subject received an oral dose of bilastine (20 or 50 mg) or matching placebo ($n = 9$ active, $n = 3$/step placebo) once a day for 14 days (Day 1–14). Subjects ($n = 12$/step) were fasted overnight prior to dosing and remained fasted until 4 h postdose on Day 1 and Day 14. Subjects were admitted to the clinical site on the day before dosing (Day −1) and were confined until discharge on Day 4 (Part I) or Day 17 (Part II).

2.2 Subjects

Subjects were eligible for inclusion in the study if they met the following criteria: males aged 20–39 years at the time of signing the informed consent, with a body mass index (BMI) of 18.5 to <25 kg/m^2 and weight of ≥50 kg, and no use of tobacco/nicotine for 90 days prior to the study drug administration. Subjects were excluded from the study if there was evidence of any of the following criteria at screening or at any time during the study: (1) any acute or chronic disease state, including but not limited to hepatic, renal, gastrointestinal, pulmonary, endocrine, cardiovascular, hematologic, neurologic, psychiatric, immunologic, oncologic, infectious disease, or any other condition determined to be clinically significant by the investigator, (2) subjects with a history of drug allergy, (3) subjects with a history of adverse effect for which they had received medical treatment including antihistamines, (4) subjects who participated in a previous clinical trial within 90 days prior to dosing, (5) subjects who had taken ketoconazole, erythromycin, cyclosporine, diltiazem, or other drug that has an inhibitory effect of P-gp, within 30 days prior to dosing, (6) subjects who had taken any medication (including prescription and over-the-counter, except for external preparation) within 14 days prior to dosing, (7) subjects who have had food or beverage containing alcohol, caffeine/xanthine, grapefruit, citrus fruit, fruit juice, cranberries, or St. John's Wort 24 h prior to dosing, (8) subjects with clinically significant abnormal findings determined by the investigator on the physical

examination, vital signs, electrocardiogram (ECG), or clinical laboratory determinations, (9) subjects who had a >2 mm wheal reaction to saline and/or <3 mm wheal reaction to histamine skin prick test (1 mg/ml) at screening, (10) positive serum test for human immunodeficiency virus, hepatitis B virus, hepatitis C virus, or Wassermann reaction at screening, (11) subjects who had a positive urine screen for alcohol or drug of abuse at screening, (12) subjects who were not willing to use appropriate contraception both during the study period and before dosing. Concomitant medication was not allowed throughout the duration of the study.

2.3 Pharmacokinetics Assessment

Blood samples for plasma bilastine concentrations were collected at predose and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16, 24, 36, 48, and 72 h postdose in Part I; and at predose and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16, and 24 h postdose on Day 1, at predose and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16, 24, 36, 48, and 72 h postdose on Day 14, and at predose on Days 8, 12, and 13 of Part II. Urine samples for measurement of bilastine were collected within 12 h prior to dosing (Part I and Day 1 of Part II) and 0–6, 6–12, 12–24, 24–36, 36–48, and 48–72 h postdose in Part I and Day 14 of Part II, and 0–6, 6–12, and 12–24 h on Day 1 in Part II.

Plasma was collected by centrifugation, and plasma and urine samples were stored at −20 °C or below until analysis. The sample analysis and processing of derived data was performed by Anapharm Europe S.L.U. (Barcelona, Spain). Bilastine concentrations were measured by reversed phase high performance liquid chromatography coupled to a tandem mass spectrometry detector (LC/MS/MS) validated using a stable isotope label (bilastine-d6) as the internal standard. In brief, bilastine and the internal standard were extracted from 50 µL human plasma and human urine by protein precipitation with methanol and acetonitrile. Separations were isocratically performed on a reversed-phase column (Waters XBridge, 3.5 µm 2.1 × 30 mm for plasma and Waters XBridge, 3.5 µm 4.6 × 50 mm for urine) at room temperature and a flow rate of 1.00 mL/min. The mobile phase was Milli-Q water and acetonitrile containing ammonium formate 1 mM and ammonium hydroxide 0.1 %. Detection was carried out by tandem mass spectrometry on API 5000 and API 4000 mass spectrometers using positive turbo ion spray ionization. The precursor and product ions used for detection were 464 → 272 for bilastine and 470 → 278 for bilastine-d6. The calibration ranges were 0.2–400 ng/ml in plasma and 5.0–5010 ng/ml in urine. In the bioanalytical method validation studies, the within-run coefficients of variation ranged between 2.74 and 10.31 % for plasma, and between 1.58 and 9.91 % for urine. The within-run percentages of nominal concentrations ranged between 96.91 and 113.33 % for plasma, and between 91.96 and 105.02 % for urine.

Concentration data of bilastine in plasma and urine were analyzed by non-compartmental methods using Phoenix™ WinNonlin® Professional version 6.1 (CERTARA, St. Louis, MO, USA). The following pharmacokinetic parameters were obtained as applicable and as appropriate for the study: C_{max}; time to reach C_{max} (t_{max}); AUC_{0-t} (obtained by the linear-linear trapezoidal method) from time zero to t hours; and AUC from time zero to infinity (AUC_{0-inf}) after single-dose administration; terminal elimination half-life ($t_{1/2}$); apparent volume of distribution (Vd/F); oral clearance (CL/F) from plasma after oral administration; cumulative percentage of unchanged drug excreted into the urine (Ae%) up to 72 h postdose; renal clearance (CLr).

2.4 Pharmacodynamics Assessment

Antihistamine activity was assessed by measurement of the surface areas of wheal and flare responses at predose (14 h prior to dosing) and 1.5, 8, 12, and 24 h postdose. At each time point, two histamine prick tests (10 mg/ml histamine in normal saline) were performed at matching sites on opposing sides of the spine. Fifteen minutes later, the wheal and flare areas were transferred onto a transparent acetate sheet. The wheal and flare areas (mm^2) were measured by intelligent planimeter KP-21C (KOIZUMI Sokki Mfg. Co., Ltd, Niigata, Japan). An average of the two sites for each time point was calculated. At each time point, inhibition % for wheal and flare was calculated against predose.

Psychomotor activities were evaluated using the digit symbol substitution test (DSST) [8] and Stanford sleepiness scale (SSS) [9]. DSST is a paper and pencil test. Subjects were instructed to fill in the correct symbol directly below given digits over 90 s. SSS consists of statements that describe individual perceptions about alertness or sleepiness. Subjects respond by selecting a descriptive phrase and entering a corresponding number (1–7). Both DSST and SSS were assessed at predose and 2 and 24 h postdose in Part I; and at predose and 2 and 24 h postdose on Days 1, 8, and 14 in Part II.

2.5 PK and PK/PD Modeling Analysis

A mixed effects (population) PK and PK/PD model was applied starting with structures similar to the existing model for bilastine [5]. Briefly, the PK model was built first by applying a mixed effects model using Part I and II data, and a PK/PD model describing the drug effect was then

developed using Part I data according to an indirect response model.

One and two compartment disposition models with first-order absorption (ka) were explored. The structural model was parameterized in terms of bilastine clearance (CL), central volume of distribution (Vc), intercompartmental clearance (Q), peripheral volume of distribution (Vp), and ka.

In all analyses, the interindividual variability (IIV) was modeled as (e.g., Eq. 1 for CL):

$$\mathrm{CL}_j = \overline{\mathrm{CL}} \cdot \exp(\eta_{j\mathrm{CL}}) \quad (1)$$

where $\eta_{j\mathrm{CL}}$ denotes the (proportional) difference between the true parameter (CLj) of individual j and the typical value ($\overline{CL}$) in the population. The IIV was modeled the same way for the other parameters. The η's are zero mean random variables with variance ω^2 (e.g. ω^2CL). The ω^2's are the diagonal elements of the inter-individual variance-covariance matrix, Ω. Alternative correlation structures were assumed between the modeled variances, thus assuming covariance between the η's.

Residual (unexplained) variability in bilastine plasma concentration was modeled as proportional, according to Eq. 2:

$$Cp_{ij} = \widetilde{Cp_{ij}} \cdot (1 + \varepsilon_{ij}) \quad (2)$$

where $\mathrm{Cp_{ij}}$ and $\widetilde{Cp_{ij}}$ are the ith measured and model predicted (true) concentrations, respectively for patient j and ε_{ij} denotes the residual intra-patient random error, distributed with zero mean and variance σ^2.

Covariate relations were explored first using standard correlation techniques versus Empirical Bayes (EB) estimates of individual subject PK and PK/PD parameters and then when applicable, for significance within population modeling. The following covariates were assessed: Age, Weight, Height, Albumin, Bilirubin, Aspartate transaminase, Alanine aminotransferase, Blood Urea Nitrogen, Alkaline Phosphatase and Serum Creatinine. The influence of covariates was evaluated by a stepwise procedure based on the likelihood ratio test using $p < 0.05$ as entry criterion. In the covariate regression model implemented within NONMEM, the continuous covariates were centered on their median values thus allowing the intercept (q1) to represent PK parameter estimate for median covariate values.

The first-order conditional estimation (FOCE) was the primary target method used to estimate population pharmacokinetic parameters for bilastine. When the data sparseness did not permit the use of this data intensive method the NONMEM first-order estimation (FO) method was used instead.

The PK model in the Japanese population was developed independently and completely, including exploration of covariate relations. Then, combination and comparison with the Caucasian population was also performed. Full parametric convergence was sought to the maximum extent feasible given the dataset.

Similar to the PK model, the PD model was established using standard statistical and diagnostic criteria for development with parametric non-linear mixed effects models. The structural PK model previously developed was at this stage linked to the PD model to characterize bilastine effect in the Japanese population.

All model outputs were processed through custom built S-Plus scripts for model diagnosis and comparisons. Furthermore, the model was then used to compare by means of the model parameters, the Japanese and Caucasian populations. Moreover, a visual predictive check overlay of the Japanese observations was performed on Caucasian expected responses.

All modeling and simulation were performed with nonlinear mixed-effects modelling software NONMEM® version 6.2 (Globomax LLC, Dublin, Ireland). These analyses were conducted by Dynakin SL (Vizcaya, Spain).

2.6 Safety Evaluation

Safety and tolerability were assessed based on physical examinations, vital signs (axillary body temperature, supine blood pressure, and supine pulse rate), resting 12-lead ECGs, standard clinical laboratory tests (hematology, blood biochemistry, urinalysis), and adverse event (AE) monitoring. Clinically significant adverse changes in any safety assessment, including symptoms and signs, vital signs, 12-lead ECGs, and clinical laboratory tests, were considered AEs. AEs were collected from the time of dosing until the end of the study. The causal relationships for all AEs were categorized by the investigator as almost certainly, probably, or possibly related, unlikely, or unrelated.

2.7 Statistical Analysis

Summary statistics were calculated for all PK parameters by dose, expressed as mean and standard deviation (SD). All subjects who received at least one dose of study drug and for whom at least one bilastine plasma concentration was measured were included in the PK analysis. In Part I, dose-proportionality was examined for natural log-transformed $C_{\max}$ and AUC using a power model. The following model was used: log(PK parameter) = $\alpha + \beta \cdot$log(dose), where α is the intercept and β is the slope of the model. Dose proportionality was concluded if the 95 % confidence interval (CI) for β included 1 and there was no statistical significance by lack-of-fit test ($p > 0.05$) [10].

Table 1 Demographics and other baseline characteristics of study subjects

Category	Single dose (Part I)				Multiple dose (Part II)		
	10 mg	20 mg	50 mg	Placebo	20 mg	50 mg	Placebo
n	9	9	9	9	9	9	6
Age (years)	29.8 (6.9)	22.9 (2.1)	23.6 (3.1)	26.4 (7.5)	25.6 (3.2)	27.6 (5.8)	27.2 (6.1)
Weight (kg)	62.12 (6.12)	61.94 (8.22)	62.30 (5.19)	67.86 (7.20)	61.51 (5.89)	64.20 (6.00)	58.08 (3.02)
Height (cm)	170.17 (7.55)	171.80 (4.70)	173.86 (5.15)	175.49 (6.91)	171.06 (6.90)	171.70 (5.87)	166.88 (3.81)
BMI (kg/m^2)	21.46 (1.42)	20.92 (1.86)	20.61 (1.40)	21.99 (1.35)	21.03 (1.64)	21.81 (2.12)	20.85 (0.83)
Histamine prick test (predose)							
Wheal (mm^2)	30.22 (12.85)	34.72 (7.78)	29.67 (8.09)	33.72 (11.68)	29.06 (8.73)	28.83 (6.67)	25.17 (6.78)
Flare (mm^2)	814.50 (377.38)	811.17 (294.13)	810.28 (176.61)	1090.44 (243.88)	796.22 (305.59)	833.33 (133.55)	864.67 (219.98)

Data for age, weight, height, BMI, and histamine prick test (area of wheal or flare at predose) are expressed as mean (SD)

BMI body mass index, *SD* standard deviation

Variables related with both antihistamine activity (% inhibition for wheal and flare versus predose) and psychomotor activities (change in DSST or SSS from predose) were expressed as mean and standard error of mean (SEM). Statistical analysis of the difference between different treatments was performed using Student's *t* test with a significance level of 5 %.

Safety data were evaluated descriptively, and AEs were described in their entirety. All randomized subjects who received at least one dose of study drug were included in the safety analyses. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA®), version 15.1.

3 Results

3.1 Study Population

The disposition of the subjects and their characteristics are summarized in Table 1. A total of 60 healthy male subjects (36 in Part I and 24 in Part II) were randomized to study treatment. All subjects completed Part I, but one subject receiving 20-mg doses of bilastine was withdrawn from the study on Day 4 due to AE (moderate gastroenteritis) in Part II. This AE was considered by the investigator to have been caused by a bacterial infection and unrelated with study drug.

3.2 Pharmacokinetics

3.2.1 Single Dose

The mean plasma concentrations of bilastine measured for 72 h after single oral doses of 10–50 mg are shown in Fig. 1. A summary of the PK parameters is shown in Table 2. Following single-dose administration of bilastine in the fasting condition, mean t_{max} values ranged from 1.1 to 1.4 h postdose. After reaching t_{max}, bilastine plasma concentrations exhibited an apparent biphasic decline, with a mean $t_{1/2}$ ranging from 11.95 to 13.86 h. The point estimates of the parameter β in the power model were 0.99 for C_{max}, AUC_{0-24}, and AUC_{0-inf}, with inclusion of 1 for each 95 % CI (Table 3), and there was no statistical significant difference by lack-of-fit test ($p > 0.05$), suggesting that PK of bilastine is linear within the dose range of 10–50 mg. Arithmetic mean of CL/F, Vd/F, Ae%, and CLr were independent of dose across the treatment dose range.

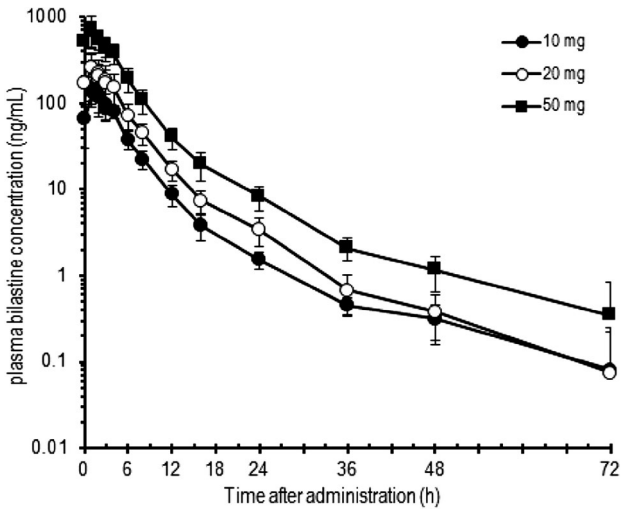

Fig. 1 Mean (±standard deviation) plasma concentrations of bilastine after single oral administration in healthy male subjects ($n = 9$/dose)

Table 2 Pharmacokinetic parameters of bilastine after a single oral dose (Part I) according to bilastine dose

Parameter	10 mg	20 mg	50 mg
C_{max} (ng/mL)	153.13 (52.47)	274.87 (109.94)	756.01 (280.06)
T_{max} (h)	1.4 (0.5)	1.4 (0.6)	1.1 (0.4)
AUC_{0-t} (ng·h/mL)	707.6 (163.3)	1366.2 (445.2)	3517.4 (921.3)
AUC_{0-inf} (ng·h/mL)	681.1 (110.6)	1372.5 (444.1)	3434.8 (922.7)
$t_{1/2}$ (h)	13.86 (9.48)	11.95 (9.05)	12.9 (8.24)
Vd/F (L)	302.44 (201.69)	286.08 (243.24)	311.64 (232.79)
CL/F (L/h)	15.05 (2.73)	16.23 (6.31)	15.72 (5.01)
Ae (%)	44.8 (12.1)	47.3 (9.8)	51.9 (10.6)
CLr (L/h)	6.37 (1.71)	7.16 (1.08)	7.62 (1.62)

Data are expressed as mean (SD)

Ae (%) cumulative percentage of bilastine excreted into the urine, *AUC* area under the plasma concentration–time curve, AUC_{0-t} AUC from time zero to time of last measurable concentration, AUC_{0-inf} AUC from time zero to infinity, *CL/F* oral clearance, *CLr* renal clearance, C_{max} maximum plasma concentration, $t_{1/2}$ terminal elimination half-life, t_{max} time to reach C_{max}, *Vd/F* apparent volume of distribution during terminal phase after non-intravenous administration

Table 3 Dose-proportionality assessment using power model

Parameter	*n*	R^2	LOF	Intercept (α)		Slope (β)	
			p value	Estimate	95% CI	Estimate	95 % CI
C_{max}	27	0.7810	0.4245	1.15	0.86–1.45	0.99	0.77–1.21
AUC_{0-t}	27	0.8461	0.6419	1.84	1.60–2.08	0.99	0.82–1.16
AUC_{0-inf}	23	0.8387	0.8512	1.83	1.55–2.10	0.99	0.80–1.19

$\log(\text{PK parameter}) = \alpha + \beta \cdot \log(\text{dose})$

AUC area under the plasma concentration–time curve, AUC_{0-t} AUC from time zero to time of last measurable concentration, AUC_{0-inf} AUC from time zero to infinity, *CI* confidence interval, *LOF* lack of fit, R^2 decision coefficient

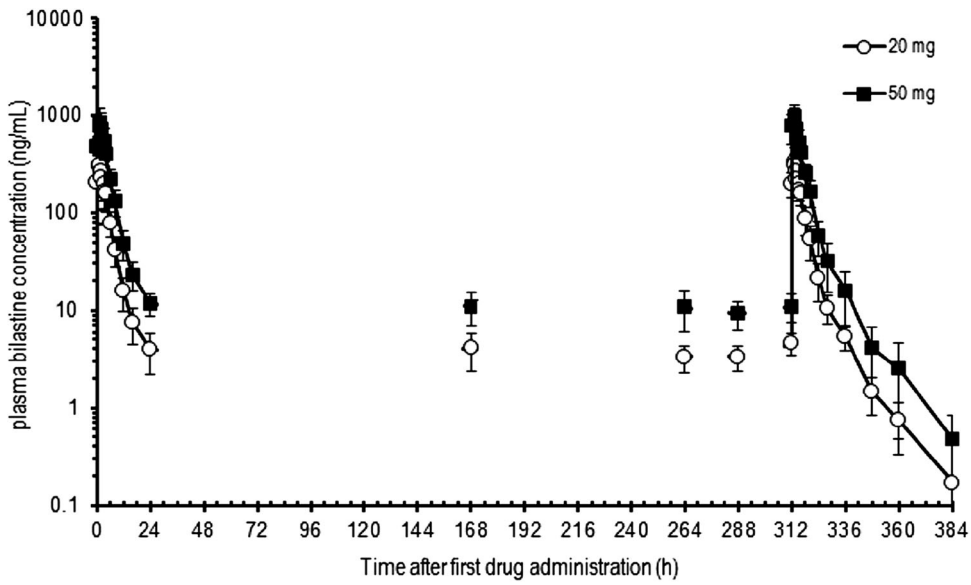

Fig. 2 Mean (±standard deviation) plasma concentrations of bilastine after multiple oral administration in healthy male subjects ($n = 8$–9/dose)

3.2.2 Multiple Dose

Mean plasma concentrations after first administration (Day 1) and repeated administration (Days 8–17) of bilastine 20 and 50 mg are shown in Fig. 2. A summary of the PK parameters of bilastine on Days 1 and 14 is shown in Table 4. After repeated administration of 20 and 50 mg, the mean minimum concentrations at steady state $[(C_{ss})_{min}]$

Table 4 Pharmacokinetic parameters of bilastine after multiple oral dose (Part II) according to bilastine dose

Parameter		20 mg	50 mg
C_{max} (ng/mL)	Day 1	344.92 (123.27)	948.50 (332.32)
	Day 14	342.32 (127.26)	1006.19 (284.17)
T_{max} (h)	Day 1	1.4 (0.5)	1.2 (0.4)
	Day 14	1.3 (0.4)	0.9 (0.2)
AUC_{0-24} (ng·h/mL)	Day 1	1439.4 (395.4)	3992.0 (1119.8)
	Day 14	1550.9 (382.1)	4474.3 (1281.1)
CLr (L/h)	Day 1	7.61 (1.43)	6.85 (1.41)
	Day 14	7.96 (1.60)	7.28 (1.77)
$t_{1/2}$ (h)	Day 14	11.56 (7.42)	10.87 (3.95)
$(Css)_{min}$ (ng/mL)		4.13 (1.13)	11.65 (4.55)
R		1.06 (0.20)	1.14 (0.20)

Data are expressed as mean (SD)

AUC area under the plasma concentration–time curve, AUC_{0-24} AUC from time zero to 24 h, *CLr* renal clearance, C_{max} maximum plasma concentration, $(Css)_{min}$ minimum plasma concentration at steady state, $t_{1/2}$ terminal elimination half-life, t_{max} time to reach C_{max}, *R* accumulation ratio (AUC_{0-24} on Day 14/AUC_{0-24} on Day 1)

were 4.13 and 11.65 ng/ml, respectively. Bilastine plasma concentrations were assessed to be at steady state within 7 days by liner regression analysis using trough plasma concentration value (Day 8, 12, 13, and 14). The accumulation ratio (*R*) of AUC_{0-24} on Day 14 to AUC_{0-24} on Day 1 was 1.06 in the 20 mg and 1.14 in the 50 mg, suggesting that bilastine does not accumulate with once-daily dosing. The mean values for C_{max}, T_{max}, CLr, and $t_{1/2}$ were similar between Days 14 and 1, indicating that there were no remarkable changes in PK parameters after repeated once-daily dosing.

3.3 Pharmacodynamics

3.3.1 Antihistamine Activity

The inhibitory effect of bilastine on histamine-induced wheal and flare response after single oral doses of 10–50 mg are shown in Fig. 3. Bilastine 20 and 50 mg showed significant inhibition of wheal (Fig. 3a) and flare responses (Fig. 3b) from 1.5 h after postdose as compared with placebo ($p < 0.001$), and the significant effect persisted for 24 h after dosing ($p < 0.001$). In particular, wheal and flare responses were almost completely inhibited by bilastine 20 and 50 mg from 1.5 to 12 h after dosing. On the other hand, bilastine 10 mg significantly inhibited wheal response at 8 and 12 h, and flare responses at 1.5, 8, and 12 h after dosing, but did not significantly inhibit wheal response at 1.5 or 24 h or flare response at 24 h after dosing. In Part II, bilastine 20

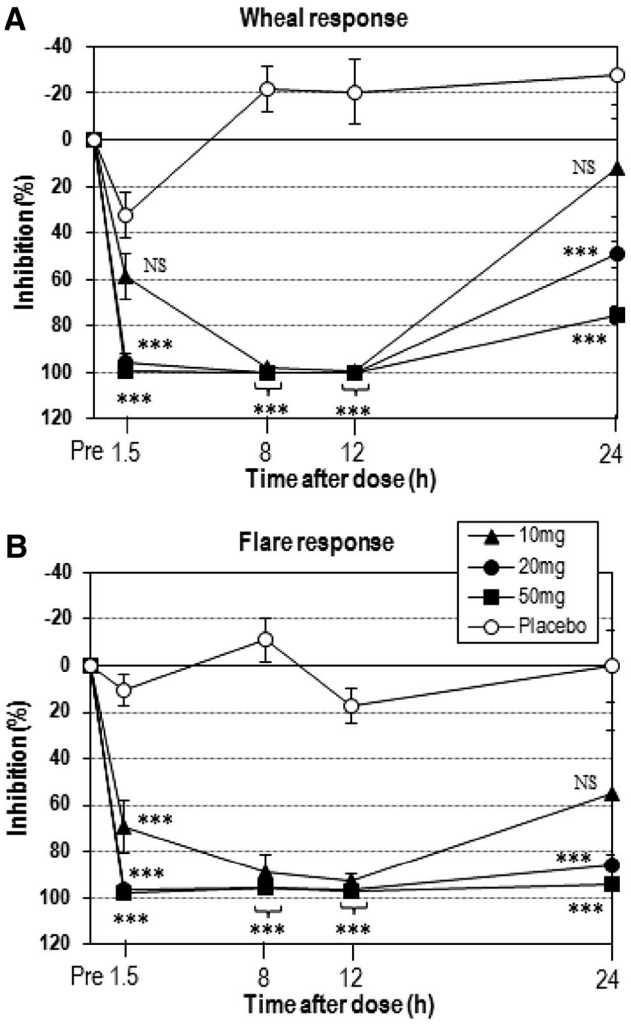

Fig. 3 Inhibitory effect of bilastine on histamine-induced wheal (**a**) and flare response (**b**) after single oral administration in healthy male subjects ($n = 9$/dose). Results are presented as mean ± SEM. ***$p < 0.001$. *NS* not significant compared with placebo (Student's *t* test)

and 50 mg also significantly inhibited wheal and flare responses from 1.5 to 24 h after dosing on Day 1, and from predose (24 h after 13th dosing) to 24 h after dosing on Day 14. Inhibitory effect of bilastine at 20 and 50 mg on wheal and flare response between Day 1 and Day 14 were of similar magnitude (data not shown).

3.3.2 Psychomotor Activity

Psychomotor activities were evaluated using objective DSST and subjective SSS. The mean ± SD of DSST and SSS at predose in Part I were 59.0 ± 8.7 and 2.2 ± 0.4 in placebo ($n = 9$), 58.6 ± 9.3 and 2.3 ± 0.9 in 10 mg ($n = 9$), 58.6 ± 9.1 and 2.7 ± 0.7 in 20 mg ($n = 9$), and 57.4 ± 8.9 and 2.9 ± 0.3 in 50 mg group ($n = 9$), respectively. Changes in DSST or SSS from predose at 2

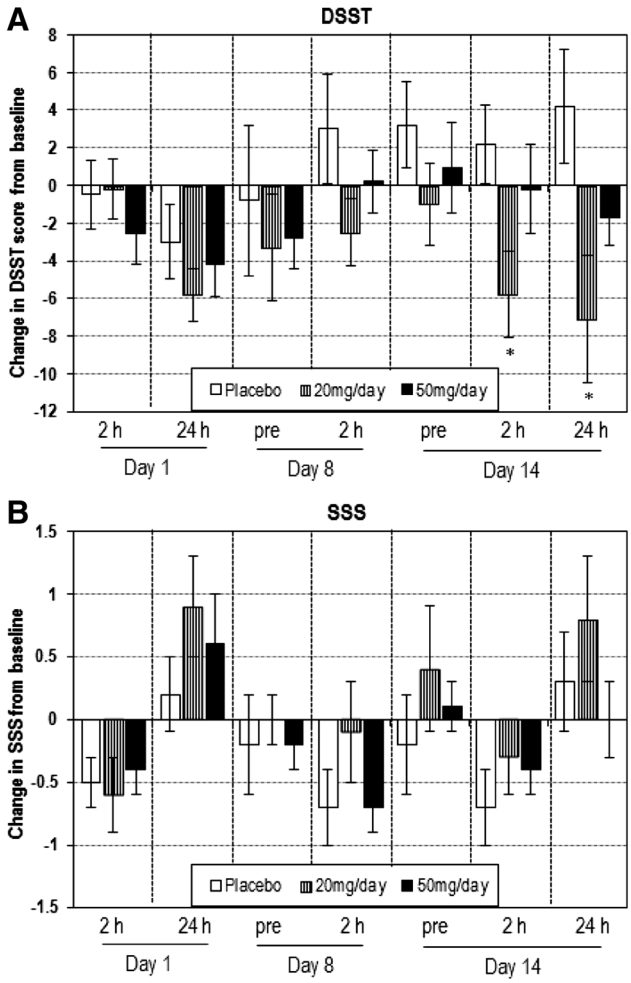

Fig. 4 Effect of bilastine on digit symbol substitution test (DSST) (**a**) and Stanford sleepiness scale (SSS) (**b**) after multiple oral administration in healthy male subjects ($n = 8$–9/bilastine, $n = 6$/placebo). Results are presented as mean ± SEM. $*p < 0.05$ compared with placebo (Student's *t* test)

and 24 h after single oral doses of 10–50 mg were not significant differences from placebo (data not shown).

The mean ± SD of DSST and SSS at predose in Part II were 56.7 ± 5.9 and 3.0 ± 0.6 in placebo ($n = 6$), 58.7 ± 6.5 and 2.3 ± 0.7 in 20 mg ($n = 9$), and 57.6 ± 9.2 and 2.8 ± 1.0 in 50 mg group ($n = 9$), respectively. Although bilastine 20 mg/day significantly decreased DSST at 2 and 24 h on Day 14, as compared with placebo, no significant differences were noted at any time points between 50 mg/day and placebo (Fig. 4a). No significant differences were observed for SSS at any time points between the drug-treated groups and placebo group (Fig. 4b).

3.4 Population PK and PK/PD Modeling Analysis

The PK model structure that best described the PK behavior in the Japanese population was a two-compartment, semi-physiological parameter PK model (the details were described in the Electronic Supplementary material). The model structure was implemented in NONMEM, including a full random effect 4 × 4 matrix for all systemic parameters (CL, Vc, Q, Vp), a separate random effect on ka, and a proportional-only residual error model. The proportional model was selected after comparison with an additive model. The additive residual error model had nearly twice the objective function compared to the proportional error model (9669.6 vs. 5487.4). No covariate effects were found in any of the pharmacokinetic parameters. The final Japanese population PK parameter estimates are shown in Table 5. All parameters, including random effects, were well estimated using this model, as evidenced by standard error of estimate (% SEE) being below 50 % in all cases.

Just as for the PK, model establishment in the Japanese population was accomplished using standard statistical and diagnostic criteria for PD model development with parametric non-linear mixed effects. Due to the sparseness of the data, model development followed an ad hoc process of sequential removal of random effects and then changing of initial estimates of the fixed effects in order to achieve convergence. The model was then used to compare the Japanese and Caucasian populations by means of the model parameters. The final PD model estimates for the wheal

Table 5 Population PK model fit to plasma concentration-time data from Japanese and Caucasian subjects

PK parameter	Japanese[a] Estimate (% SEE)	Caucasian[b] [5] Estimate (% SEE)
CL (L/h)	14.4 (4)	18.1 (1.8)
Vc (L)	51.2 (5)	59.2 (2.2)
Q (L/h)	1.55 (8)	1.59 (3.9)
Vp (L)	20.2 (9)	30.2 (5.1)
ka (h^{-1})	1.7 (7)	1.5 (3.2)
Inter-individual variability		
ωCL (%)	28 (22)	29.0 (8.7)
ωVc (%)	34 (19)	35.4 (9.6)
ωQ (%)	50 (27)	56.5 (10.3)
ωVp (%)	61 (21)	73.1 (9.6)
ωka (%)	28 (40)	35.4 (16.9)
Residual variability		
σ (%)	21 (9)	28.6 (6.1)

CL apparent total clearance of the drug from plasma, *ka* first-order absorption rate constant, *Q* intercompartmental clearance, *Vc* central compartment volume of distribution, *Vp* peripheral compartment volume of distribution, *SEE* standard error of estimate

[a] Population pharmacokinetic parameters estimated from Japanese data in this study ($n = 45$, 1022 plasma observations)

[b] Caucasian data originated from a previous report [5] ($n = 310$, 8429 plasma observations), permission obtained from Springer Science + Business Media

Table 6 Pharmacokinetic-pharmacodynamic population model fit of the inhibitory effect on wheal and flare response in Japanese and Caucasian subjects

Parameter	Japanese[a] Estimate (% SEE)	Caucasian[b] [5] Estimate (% SEE)
Wheal		
K_{on} (cm^2/h)	0.84 (4)	0.44 (14.6)
K_{off} (h^{-1})	1.72 (7)	1.09 (15.14)
IC_{50} (ng/mL)	1.03 (11)	5.15 (16.16)
Flare		
K_{on} (cm^2/h)	13.9 (NA)	11.10 (8.48)
K_{off} (h^{-1})	1.67 (NA)	1.03 (8.35)
IC_{50} (ng/mL)	0.35 (NA)	1.25 (14.56)

IC_{50} estimated concentration producing 50 % inhibition, *K_{on}* zero-order rate constant for production of response, *K_{off}* first-order rate for loss of response, *NA* not applicable, *SEE* standard error of estimate

[a] Population pharmacokinetic parameters estimated from Japanese data in Part I of this study ($n = 27$)

[b] Caucasian data originated from a previous report [5] ($n = 53$), permission obtained from Springer Science + Business Media

and flare response in the Japanese population are summarized in Table 6. The population distribution parameters were well estimated using NONMEM® with % SEE less than 50 % for wheal response. In spite of using different concentration of histamine (10 mg/ml for Japanese, 100 mg/ml for Caucasians), the effect onset (K_{on}) and reset (K_{off}) parameters are of similar order between Caucasians and Japanese, and their ratios (K_{on}/K_{off} : starting baseline of extent) are very similar (0.49 in Japanese vs. 0.40 in Caucasians for wheal response, 8.32 in Japanese vs. 10.78 in Caucasians for flare response). The estimated plasma bilastine concentration producing 50 % inhibition (IC_{50}) for wheal and flare response in healthy Japanese subjects was 1.03 and 0.35 ng/ml, respectively.

3.5 Safety

In Part I, 3 AEs were reported by three of the 36 subjects (nine subjects/dose): two subjects (22.2 %) in the 20-mg group, and one subject (11.1 %) in the 50-mg group. No AEs were observed in the placebo or 10-mg groups. All reported AEs [dizziness ($n = 2$ in 20 mg), diarrhea ($n = 1$ in 50 mg)] were mild in severity, and were deemed possibly related to the study drug. In Part II, 13 AEs were reported by 13 of the 24 subjects (six subjects/placebo, nine subjects/bilastine): four (66.7 %) in the placebo, five (55.6 %) in the 20 mg/day, and four subjects (44.4 %) in the 50 mg/day group. Most reported AEs were mild in severity, except for moderate gastroenteritis in the 20 mg/day group. One subject who reported moderate gastroenteritis was withdrawn from the study on Day 4. Seven of the 13 AEs were considered by the investigator to be possibly related to the study drug; diarrhea ($n = 1$) and eczema ($n = 1$) in the placebo, diarrhea ($n = 1$) and stomatitis ($n = 1$) in the 20 mg/day, and glossitis ($n = 1$), epistaxis ($n = 1$), and eczema ($n = 1$) in the 50 mg/day group. No subject death or other serious adverse events were reported in either part. Throughout the single- and multiple-dose periods, no clinically significant changes in hematology, chemistry laboratory test, or 12-lead ECG results were observed.

4 Discussion

Bilastine was approved in 2010 by countries in Europe for symptomatic treatment of allergic rhinoconjunctivitis and urticaria [1], but has not yet been approved in Japan. This study was conducted as the first bilastine PK/PD study to evaluate the single- and multiple-dose PK, PD, safety, and tolerability of bilastine in healthy Japanese subjects. Population PK and PK/PD analyses of bilastine in this study were performed to evaluate the ethnic differences between Japanese and Caucasian subjects, in support of the clinical development of bilastine in Japan.

Comparison of bilastine PK parameters in Japanese and Caucasians was conducted using population PK modeling. The PK model structure in the Japanese population that best described the data was a two-compartment, semi-physiological parameter PK model, which was identical to that previously reported for a Caucasian population [5]. Moreover, PK parameters in the Japanese population (both structural and statistical) were similar to those of the Caucasian PK behavior by using the mixture distribution modeling (data not shown), whereas inter-individual variability was of medium magnitude and comparable to the Caucasian population (Table 5). The visual predictive check was also performed by overlaying Japanese plasma concentrations (observations after 20 mg dose; recommended dose outside Japan) on the 95 % CI of the predicted PK in the Caucasian population at the same dose. Less than 10 % of Japanese observations out of the entire dataset were outside the 95 % CI of the predicted distribution for the Caucasian population, both after first (Day 1) and repeated administration (Day 14), confirming statistically the homogeneity of the two populations (data not shown). These results led to the conclusion that the two groups, Japanese and Caucasian, do not differ with respect to the distributional properties of bilastine PK parameters.

The onset of action of a single administration of bilastine on histamine-induced wheal and flare response was very rapid, within 1.5 h postdose. The peak effect was the same for all dose levels at maximum inhibition of reaction,

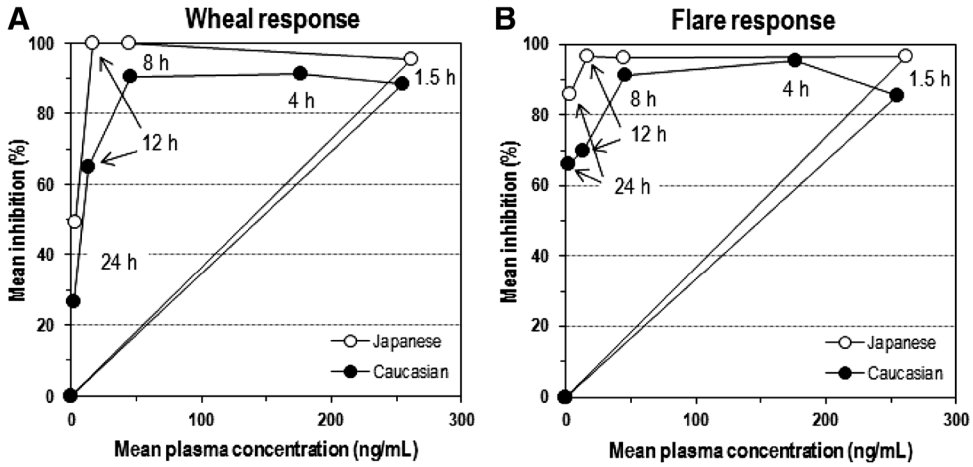

Fig. 5 Hysteresis plots of inhibition of histamine-induced wheal (**a**) and flare responses (**b**) against plasma concentration following single oral administration of bilastine 20 mg in healthy Japanese and Caucasian subjects. Each point is the mean of measurements in nine (Japanese) or 12 subjects (Caucasian). Caucasian data originated from a previous report [11] (permission obtained from Springer Science + Business Media)

showing that it is a very effective drug reaching 100 % inhibition. On the other hand, bilastine 10 mg did not significantly inhibit wheal response at 1.5 or 24 h, or flare response at 24 h postdose as compared with placebo, suggesting that onset and duration of action at 10 mg are inferior to ≥20 mg dose. These results were similar to previous reports in healthy Caucasian subjects [5, 11].

The PK/PD modeling of the wheal and flare response was developed in the Japanese population using single-administration data. The PK/PD modeling from the Japanese subjects was complicated. No random effects could be estimated for wheal, but a naïve pooled population model was possible. However, for flare, a profiling method was used to arrive at a possible naïve pooled minimum. The difficulties found during the modeling processes were mainly due to: (a) the small sample size, (b) the saturation effect (near E_{max}) with weak reset (K_{off}) at higher doses within the studied time period, and (c) the study time range, which did not include return to baseline. Nevertheless, it was possible to extract the following information from the analysis: (1) Similar K_{on}/K_{off} parameter ratios between Caucasians and Japanese in the inhibitory response models for both wheal and flare effects, (2) when comparing with empirical Bayesian individual parameter distributions, similar indirect effect parameters were obtained between Caucasians and Japanese for flare, and were of the same order of magnitude in the case of the wheal effect.

To assess the relationship between the PK and PD after 20 mg of bilastine in both Japanese and healthy Caucasian subjects, hysteresis plots for inhibition of the wheal and flare responses against plasma concentration were plotted (Fig. 5). The results show slight differences in inhibition rates of wheal and flare responses between the Japanese and Caucasian subjects; however, the onset and the time course of antihistamine activity, and plasma drug concentrations after administration of 20 mg showed visually similar patterns. Although use of histamine-induced wheal and flare reaction is well known in PD research of antihistamines as a useful clinical pharmacologic test to assess dose-response relations of or among antihistamines and to correlate the test results with plasma levels of the drugs, it was reported that the lack of correlation with clinical responses among antihistamines in this model indicates that the model should not be used to predict or compare clinical efficacies of antihistamines in seasonal allergic rhinitis or chronic idiopathic urticaria [12]. Therefore, it could be concluded that the antihistamine activity of bilastine in the Japanese population was similar to that in Caucasians; however, a dose-response study is needed for Japanese patients with allergic rhinitis or chronic urticaria (Fig. 5).

In the present study, no case of somnolence, a known adverse drug reaction (ADR) caused by antihistamines (class effect), was reported. As an exploratory analysis for the study, objective and subjective psychomotor activity were evaluated using DSST and SSS, respectively. Although significant differences in change in DSST score from baseline were observed at 2 and 24 h after repeated administration of 20 mg/day on Day 14, none of the bilastine doses (ranging from 10–50 mg) showed significant difference from placebo in DSST or SSS, indicating that bilastine has almost no effect on psychomotor activity in healthy Japanese subjects.

In both single- and multiple-dose administration, the rates of AEs were comparable between the bilastine and placebo groups. In addition, no dose- or administration period-dependent tendency for increase in rate of AEs or worsening of severity was observed. No noteworthy events were observed in comparison with ADRs reported outside of Japan [1]. Although one subject reported moderate gastroenteritis in repeated administration of 20 mg and was discontinued from study treatment, the causal relationship with the study drug was ruled out, and thus it was deemed that there was no safety concern with bilastine. Other AEs were all mild in severity. Therefore, bilastine was safe and

well tolerated in the healthy Japanese subjects in the present study.

5 Conclusions

Bilastine is rapidly absorbed after oral administration, with time to maximum plasma concentration of around 1 h under fasting conditions, and shows linear PK over a dose range of 10–50 mg. Steady-state conditions were reached within 7 days of once-daily administration with bilastine, and no accumulation or obvious changes in PK parameters were observed. Bilastine exhibited similar single- and multiple-dose pharmacokinetic and pharmacodynamic characteristics in healthy Japanese subjects compared with those observed in Caucasian subjects in previous studies. Bilastine was also safe and well tolerated in healthy Japanese subjects.

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Compliance with Ethical Standards

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Conflict of interest M Togawa, and H. Yamaya are paid employees of TAIHO Pharmaceutical Co. Ltd. Dr. Monica Rodríguez carried out PK/PD modeling, and Dr. Nagashima was the principal investigator in this study, for which they received financial compensation from TAIHO. The authors have indicated that they have no other conflicts of interest with regard to the content of this article.

Ethics All procedures in this study were performed in accordance with the ethical standards of the institutional and/or the institutional review board, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants prior to their inclusion in the study.

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