

Influence of Taranabant, a Cannabinoid-1 Receptor Inverse Agonist, on Pharmacokinetics and Pharmacodynamics of Warfarin

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ABSTRACT

Introduction: The pharmacokinetic/pharmacodynamic effects of warfarin were assessed in the presence and absence of taranabant, an orally active, highly selective, potent, cannabinoid-1 receptor inverse agonist, which was being developed for the treatment of obesity.

Methods: Twelve subjects were assigned to two open-label treatments in fixed sequence separated by a 14-day washout. Treatment A was single-dose warfarin 30 mg on day 1. Treatment B was multiple-dose taranabant 6 mg each day for 21 days (days -14 to day 7) with coadministration of single-dose warfarin 30 mg on day 1. Blood samples were collected predose and up to 168 hours postdose for assay of R(+)- and S(-)-warfarin and prothrombin time/international normalized ratio (PT/INR).

Results: The geometric mean ratios (GMR; warfarin+taranabant/warfarin 90% confidence interval [CI] primary endpoints) for area under the curve ($AUC_{0-\infty}$) for R(+)- and S(-)-warfarin were 1.10 (90% CI: 1.03, 1.18) and 1.06 (90% CI: 1.00, 1.13), respectively. The GMRs (warfarin+taranabant/warfarin) for the maximum plasma concentration (C_{max}) of S(-)- and R(+)-warfarin were 1.16 (90% CI: 1.05, 1.28) and 1.17 (90% CI: 1.07, 1.29), respectively. For R(+)- and S(-)-warfarin, the 90% CIs for $AUC_{0-\infty}$ GMRs fell within the prespecified bounds. Taranabant did not produce a clinically meaningful effect on PT/INR.

Conclusion: No clinically significant alterations of the pharmacokinetics of R(+)- and S(-)-warfarin were seen following coadministration of multiple-dose taranabant 6 mg and single-dose warfarin 30 mg.

Keywords: cannabinoid-1 receptor inverse agonist; CB1R; obesity; pharmacodynamics; pharmacokinetics; taranabant; warfarin

INTRODUCTION

Obese (body mass index [BMI] ≥ 30 kg/m²) and overweight (BMI ≥ 25 and < 30 kg/m²) individuals are at high risk of developing serious chronic health problems including diabetes, hypertension, dyslipidemia, and cardiovascular disease.¹ Caloric restriction and increased physical activity remain the primary treatment options for

management of body weight in these individuals.² Body weight reduction can lead to a compensatory decrease in metabolic rate, making weight loss difficult to maintain by caloric restriction alone. A medical need exists for the development of long-term weight loss therapies that simultaneously reduce caloric intake (ie, appetite) and also promote energy expenditure through increases in the body's metabolic rate.

Cannabinoid-1 receptor (CB1R) inverse agonists represent a new therapeutic approach for the treatment of obesity. Endocannabinoids regulate whole-body energy balance through the activation of G protein-coupled CB1Rs located in the central nervous system, which lead to increased appetite and food intake.³⁻⁶ In contrast, CB1R inverse agonists have been shown to induce weight loss by inhibiting food intake and increasing energy expenditure.⁷

An orally active, highly selective, potent CB1R inverse agonist, taranabant (also known as MK-0364), was under development as a potential new therapy for the treatment of obesity.⁸ In animal models of obesity, taranabant inhibited food intake and weight regain in a dose-dependent manner, resulting in significant weight loss and decreased fat mass.⁹ In overweight and obese male volunteers, taranabant reduced food intake over 24 hours and significantly increased energy expenditure between 2 to 5 hours postdose compared with placebo.⁷ Recent results from phase 2 and 3 clinical trials showed that the administration of taranabant in doses ranging from 0.5 to 6 mg led to clinically significant, dose-dependent reductions in body weight and waist circumference in obese and overweight adults.^{7,10}

Warfarin, a commonly prescribed coumarin-based anticoagulant, is indicated for use in patients at risk of thrombotic and embolic disorders.¹¹ Warfarin reduces coagulation by interfering with the vitamin K-dependent posttranslational modification of several coagulation and fibrinolytic factors.¹¹ It is administered as a racemic formulation of R(+)- and S(-)-

warfarin enantiomers. The anticoagulant potency of the S(-)-enantiomer is approximately 5 to 6 times greater than that of the R(+)-enantiomer, whereas S(-)-warfarin possesses a shorter plasma half-life (32 vs. 43 hours, respectively).¹² The efficacy of warfarin therapy can be effectively monitored by the measurement of prothrombin time (PT) converted to the standardized parameter of the international normalized ratio (INR).¹³ Fluctuations in a patient's anticoagulant state during warfarin treatment, as reflected by PT/INR, can lead to serious clinical consequences, including excessive bleeding and thrombosis, and therefore warrants close monitoring.¹¹

Warfarin has a narrow therapeutic index and sufficient alterations in its pharmacokinetics can lead to clinically important changes in warfarin pharmacodynamics, as measured by PT/INR.¹¹ Warfarin is largely metabolized by hepatic microsomal enzymes, with cytochrome P-450 (CYP) 2C9 being primarily responsible for the oxidative conversion of the (S)-enantiomer to (S)-7-hydroxywarfarin and, to a limited extent, (S)-6-hydroxywarfarin.^{12,14,15} In contrast, no single enzyme dominates the metabolism of the less-potent warfarin enantiomer (R)-warfarin.^{12,14} The major contributors to oxidative metabolism of (R)-warfarin include CYP 3A4, 2C19, and 1A2.^{12,14} Changes in the activities of any one of these CYP isoenzymes would not be anticipated to have a significant effect on the metabolic clearance of (R)-warfarin, given its multiple clearance pathways.

Taranabant is rapidly absorbed (median time to maximum plasma concentra-

tion [T_{\max}] within 1 to 2.5 hours postdose), with plasma concentrations then declining in a biphasic manner: an initial rapid decline from approximately 2 hours postdose, followed by a slower phase.¹⁶ Its apparent terminal half-life ($t_{1/2}$) averages approximately 70 hours.¹⁶ Following single oral-dose administration, the pharmacokinetics of taranabant have been found to be approximately dose-proportional over the dose range from 1.0 to 200 mg.¹⁶ After multiple-dose administration, a steady state is generally reached within 9-13 days with modest accumulation (1.5 to 1.9 in area under the curve [AUC]_{0-24hours}).¹⁷ Research has shown that taranabant steady-state $AUC_{0-24hours}$ and maximum plasma concentration (C_{\max}) values increase linearly with once-daily doses up to 10 mg; there is no evidence of auto-induction within this dose range.¹⁷

Previous in-vitro and clinical studies have shown that taranabant is extensively metabolized by CYP 3A4,¹⁸ and is minimally excreted in urine.¹⁶ In human hepatic microsomes, taranabant and its M1 metabolite inhibit CYP 3A4 with IC50 values of 3.4 μ M and 1.3 μ M, respectively (Merck & Co, Inc., data on file, 2008). IC50 values against CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 2E1-mediated reactions were >100, 79, 24, 9.8, 39, 8.5, and >100 μ M for taranabant, and >100, 11, 17, 6.7, 36, 6.7, and >100 μ M for M1, respectively (Merck & Co, Inc., data on file, 2008). However, taranabant did not change the pharmacokinetic profile of midazolam, a probe substrate of CYP 3A4, indicating that taranabant does not inhibit CYP 3A4 in vivo.¹⁹ Since taranabant and M1 are much weaker inhibitors of other

CYPs in vitro, clinically significant drug interactions due to inhibition of any P450 are not anticipated. The metabolic pathways suspected to be responsible for the biotransformation of the less-potent R(+)-warfarin enantiomer include CYP 3A4, CYP 1A2, and CYP 2C19, whereas the more-potent S(-)-warfarin enantiomer is oxidized primarily by CYP 2C9.^{12,14,15} Based on the known pharmacology of taranabant and warfarin, coadministration of steady-state taranabant with single-dose warfarin 30 mg was not expected to have a clinically meaningful effect on the pharmacokinetics of S(-)- or R(+)-warfarin.

This study assessed the potential influence of taranabant on the pharmacokinetics of (S)- and (R)-warfarin due to the high likelihood that these two compounds will be concomitantly administered in clinical practice. The main objective of this study was to evaluate the potential effects of taranabant (6 mg dosed to steady state) on the pharmacokinetics (primary endpoint: $AUC_{0-\infty}$; secondary endpoint: C_{\max}) and pharmacodynamics (PT/INR) of single-dose warfarin in healthy male and female subjects. The safety and tolerability profile of the combined administration of taranabant and warfarin also was examined in this study.

MATERIALS AND METHODS

Subjects

Eligible participants included healthy, nonsmoking, male subjects, and nonpregnant female subjects of non-childbearing potential (ie, hysterectomy, bilateral oo-

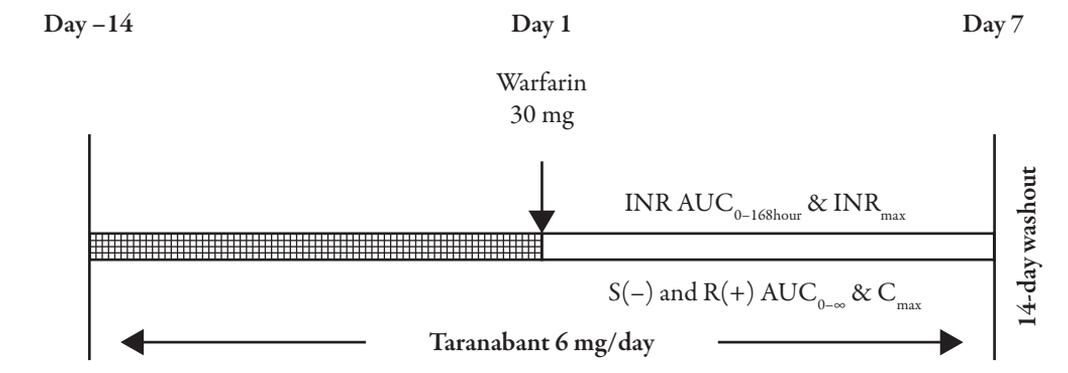
phorectomy, tubal ligation, or postmenopausal) between 18 to 50 years of age with a BMI between 18.5 and 32 kg/m² who agreed to comply with all study restrictions. Additional entry criteria included normal prestudy laboratory test results for PT, activated partial thromboplastin time, platelet count, and negative stool occult blood test. Subjects could not be involved with any activities that would place them at high-risk of hemorrhage (eg, contact sports). Subjects also had to agree to restrict their intake of alcohol, caffeinated beverages, grapefruit, grapefruit juice, and quinine-containing beverages. Subjects were excluded if they had any relevant history of pulmonary, hepatic, gastrointestinal, psychiatric, or neurologic disease; diabetes; any condition predisposing them to immunodeficiency; and any condition contraindicating use of warfarin (eg, hemorrhagic tendencies, recent or pending surgery, ulceration or overt bleeding of gastrointestinal system). Subjects with an estimated creatinine clearance of ≤ 60

mL/min or serum creatinine >1.5 mg/dL were excluded. Additional exclusion criteria included a history of multiple and/or severe allergies to drugs or foods.

Study Design

This open-label, fixed-sequence, crossover study consisted of two consecutive treatment periods beginning with Treatment A in period 1 followed by Treatment B in period 2 (Figure 1). Treatment A consisted of a single open-label oral dose of warfarin 30 mg (Coumadin[™]; Bristol-Myers Squibb Company, NY, USA; administered as 6 \times 5 mg) on day 1. It was important to ensure that plasma concentrations of taranabant reached steady state prior to administration of single-dose warfarin in this study. Previous pharmacokinetic studies indicated that steady state for taranabant is achieved by 14 days of once-daily dosing of healthy young males and females.¹⁷ In addition, the maximum daily dose in late-phase safety and efficacy

Figure 1. Study design schematic. Treatment A=single-dose warfarin 30 mg on day 1. Treatment B=once-daily open-label dosing of taranabant 6 mg for 21 days (day -14 to day 7) with coadministration of a single open-label oral dose of warfarin 30 mg (6 \times 5 mg) on day 1. AUC=area under the curve; C_{max}=maximum plasma concentration; INR=international normalized ratio.



studies was 6 mg. Therefore, Treatment B consisted of once-daily open-label dosing of taranabant 6 mg for 21 days (day -14 to day 7) with coadministration of a single open-label oral dose of warfarin 30 mg (6×5 mg) on day 1. There was a 14-day washout interval between the dose of warfarin in period 1 and the first dose of taranabant in period 2 (see Figure 1). The doses on day 1 for both treatment periods were administered with 240 mL of water in the morning following an overnight fast with water intake restricted 1 hour before and after study drug administration.

The use of prescription and nonprescription medications was not allowed within 14 days of study start and throughout the entire study period. Subjects could be discontinued from the study for the following predefined reasons: any adverse experience that jeopardized the subject's safety and/or well-being; deviation from dosing regimen; use of excluded concomitant medications; and positive or borderline pregnancy test results.

This study was conducted at a single study center in the United States. Each subject provided written informed consent prior to the administration of study procedures. The study protocol was approved by the Independent Ethics Committee and was conducted in accordance with the guidelines established by the Declaration of Helsinki.

Pharmacokinetic Assessments

Blood (4 mL) was drawn in sodium heparin-containing tubes predose on day 1 and postdose at 0.5, 1, 2, 4, 12, 24, 48,

72, 96, 120, 144, and 168 hours for measurement of S(-)- and R(+)-enantiomers of warfarin. Plasma was prepared and stored at -20°C until assayed and shipped on dry ice to a central laboratory (Advion BioScience, Inc., Ithaca, NY, USA) for assay. Pharmacokinetic parameters were calculated using WinNonlin Version 5.0.1 (Pharsight Corporation, Mountain View, CA, USA). Apparent terminal rate constant (λ) was estimated from the terminal portion of the log-transformed plasma concentration-time profile using linear regression. $T_{1/2}$ was calculated as the product of $\ln(2)/\lambda$. The AUC to the last time point with a detectable plasma concentration (AUC_{0-last}) was calculated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations. $AUC_{0-\infty}$ ($\mu\text{M}/\text{hour}$) was estimated as the sum of AUC to the last measured concentration and the extrapolated area given by the quotient of the last measured concentration and λ . Peak plasma concentration (C_{max} [μM]) and its time of occurrence (T_{max} [hours]) were obtained by inspection of the plasma concentration-time profile.

Pharmacodynamic Assessments

The pharmacodynamics of warfarin were evaluated through measurement of PT and calculation of INR using a single lot of thromboplastin with international sensitivity index, at various time points throughout the study. All measurements of PT and calculations of INR were done at the site's local laboratory. Blood samples (3 mL) for PT/INR measurement were

collected predose on day 1, and 1, 2, 4, 12, 24, 48, 72, 96, 120, 144, and 168 hours postdose. Plasma was prepared and used for PT determination in duplicate within 2 hours of collection. PTs were reported both as raw data in absolute time (seconds) and as INRs.

Analytical Methods

A sensitive, specific, accurate, and reproducible analytical method was developed by Advion BioSciences, Inc. (Ithaca, NY, USA) to quantitate total (R)-warfarin and (S)-warfarin in heparinized human plasma samples. Plasma samples (0.1 mL) were diluted with citric acid, centrifuged, and injected onto a column switching system where the two enantiomers were separated chromatographically using a chiral column following clean-up on a semipermeable-surface -Ph trapping column. Samples were analyzed by turbo ion spray, column switching, liquid chromatography/tandem mass spectrometry (LC/LC/MS/MS) in the negative ion mode. The assay demonstrated a lower limit of quantitation (LLQ) of 10 ng/mL using 0.1 mL plasma sample aliquots. The calibration curves were linear from 10 ng/mL to 2500 ng/mL for (R)- and (S)-warfarin.

Safety Measurements

The safety and tolerability of study medication was assessed by clinical evaluation of adverse experiences and inspection of other safety parameters including physical examinations, vital signs, routine laboratory safety measurements (hema-

tology, blood chemistry, and urinalysis), serum beta-human chorionic gonadotropin, and 12-lead electrocardiograms. Adverse experiences were monitored throughout the study and evaluated in terms of intensity (mild, moderate, or severe), duration, severity, outcome, and relationship to study drug. All subjects who took at least one dose of study medication (Treatment A or B) were included in the safety/tolerability analyses.

Statistical Analysis

Primary and secondary pharmacokinetic endpoints in this study included $AUC_{0-\infty}$ and C_{max} values, respectively, for S(-)- and R(+)-warfarin. The primary study hypothesis stated that multiple-dose taranabant 6 mg (21 days) would not substantially alter the single-dose plasma pharmacokinetics of warfarin 30 mg as assessed by measurement of S(-)- and R(+)-warfarin $AUC_{0-\infty}$ in the absence and presence of taranabant (ie, the true geometric mean ratios [GMRs] and 90% CIs warfarin+taranabant/warfarin for the plasma $AUC_{0-\infty}$ of S(-)- and R(+)-warfarin enantiomers would be contained within the prespecified comparability bounds [0.80, 1.25]). The secondary study hypothesis stated that multiple-dose taranabant 6 mg (21 days) would not substantially alter the plasma C_{max} of S(-)- and R(+)-warfarin (ie, the true GMRs for the plasma C_{max} of S(-)- and R(+)-warfarin enantiomers would be contained within the prespecified comparability bounds [0.80, 1.25]).

The $AUC_{0-\infty}$ and C_{\max} values were analyzed after transformation to the natural log scale. A mixed model appropriate for a two-period fixed-sequence study design was used to compare the pharmacokinetic parameters of S(-)- and R(+)-warfarin in the absence and presence of taranabant. The model included terms for subject (random effect) and treatment (fixed effect). This model assumed that the time and/or period effects were negligible since they cannot be distinguished from the treatment effect. A two one-sided testing procedure, in which the confidence level (α) was set to 5% per test, for an overall studywise type I error rate of up to 5%, was implemented to assess the hypothesis.^{20,21} The test proceeded as follows: 1) 90% CIs were constructed for the GMRs (warfarin+taranabant/warfarin) for warfarin S(-) and R(+) $AUC_{0-\infty}$ and C_{\max} from the model after back transformation of the difference between means; 2) If the 90% CIs for both the GMRs of warfarin S(-) and R(+) $AUC_{0-\infty}$ were contained within the prespecified bounds (0.80, 1.25), then the primary study hypothesis was supported. Similarly, if the 90% CIs for both the GMRs of warfarin S(-) and R(+) C_{\max} were contained within the prespecified bounds (0.80, 1.25), then the secondary study hypothesis was supported. Results for T_{\max} were summarized by providing medians and estimates for median differences using Hodges-Lehmann point estimation. Harmonic mean was provided for apparent $t_{1/2}$.

The influence of multiple-dose taranabant on the pharmacodynamics of single-dose warfarin was assessed through the measurement of INR $AUC_{0-168\text{hours}}$

and INR_{\max} for PT and analyzed using the same mixed model as described above for the pharmacokinetic analyses. The natural log transformation was applied to both of these parameters prior to analysis. Summary statistics and 90% CIs for INR $AUC_{0-168\text{hours}}$ and INR_{\max} GMRs (warfarin+taranabant/warfarin) were provided.

RESULTS

Study Population

Baseline demographics of the study participants are presented in Table 1. All 12 subjects were Hispanic. Eleven (92%) subjects completed the study per protocol. One subject was discontinued from the study due to a protocol deviation (ie, positive drug screen at admission in period 2) and was not included in the pharmacokinetic analyses.

Plasma Pharmacokinetics

The mean plasma concentration-time curves for S(-)- and R(+)-warfarin following treatment with single-dose warfarin 30 mg administered in the absence and presence of steady-state taranabant 6 mg (multiple once-daily dosing for 21 days) are illustrated in Figure 2. Summary statistics for the pharmacokinetic parameters ($AUC_{0-\infty}$, C_{\max} , T_{\max} , and $t_{1/2}$) as well as the associated GMRs (90% CI) of S(-)- and R(+)-warfarin are provided in Table 2. T_{\max} and $t_{1/2}$ of S(-)- and R(+)-warfarin (exploratory endpoints) were similar across the two treatments.

Table 1. Baseline demographics.

	All subjects (n=12)	Male (n=6)	Female (n=6)
Race, n (%)			
White	0	0	0
Black	0	0	0
Hispanic	12 (100)	6 (100)	6 (100)
Age, mean, years (range)	39.0 (19-48)	36.5 (19-48)	41.5 (30-48)
Height, mean, cm (range)	165.9 (147.3-180.3)	172.7 (167.6-180.3)	159.2 (147.3-167.6)
Weight, mean, kg (range)	75.5 (59.1-90.5)	80.5 (63.6-90.5)	70.5 (59.1-82.7)

Table 2. Pharmacokinetic parameters of R(+)- and S(-)-warfarin following administration of single-dose warfarin 30 mg alone (Treatment A) or in combination with multiple-dose taranabant 6 mg (Treatment B) in healthy subjects.

Pharmacokinetic parameter	n	Least-squares geometric mean (95% CI)		
		Warfarin alone (Treatment A)	Coadministered warfarin+taranabant (Treatment B)	Least-squares GMR (90% CI)‡
R(+)-warfarin				
AUC _{0-∞} , μM/hour†	11	306.2 (268.7, 349.0)	325.2 (285.3, 370.6)	1.06 (1.00, 1.13)
C _{max} , μM†	11	6.6 (5.5, 8.0)	7.7 (6.4, 9.4)	1.17 (1.07, 1.29)
T _{max} , hour¶	11	1.0 (0.5, 4.0)	0.5 (0.5, 2.0)	-0.5 (-1.5, 0.5)§
Apparent t _{1/2} , hour#	11	42 (8.3)	46.1 (9.1)	NC
S(-)-warfarin				
AUC _{0-∞} , μM/hour†	11	182.1 (153.3, 216.3)	200.7 (168.9, 238.4)	1.10 (1.03, 1.18)
C _{max} , μM†	11	7.0 (5.8, 8.3)	8.0 (6.7, 9.6)	1.16 (1.05, 1.28)
T _{max} , hour¶	11	1.0 (0.5, 2.0)	0.5 (0.5, 1.0)	-0.3 (-1.0, 0.5)§
Apparent t _{1/2} , hour#	11	32.2 (4.9)	34.6 (8.1)	NC

†Expressed as least-squares geometric mean (95% CI) for AUC_{0-∞} and C_{max}.

‡GMR for warfarin+taranabant/warfarin alone.

¶Expressed as median (minimum, maximum) for T_{max}.

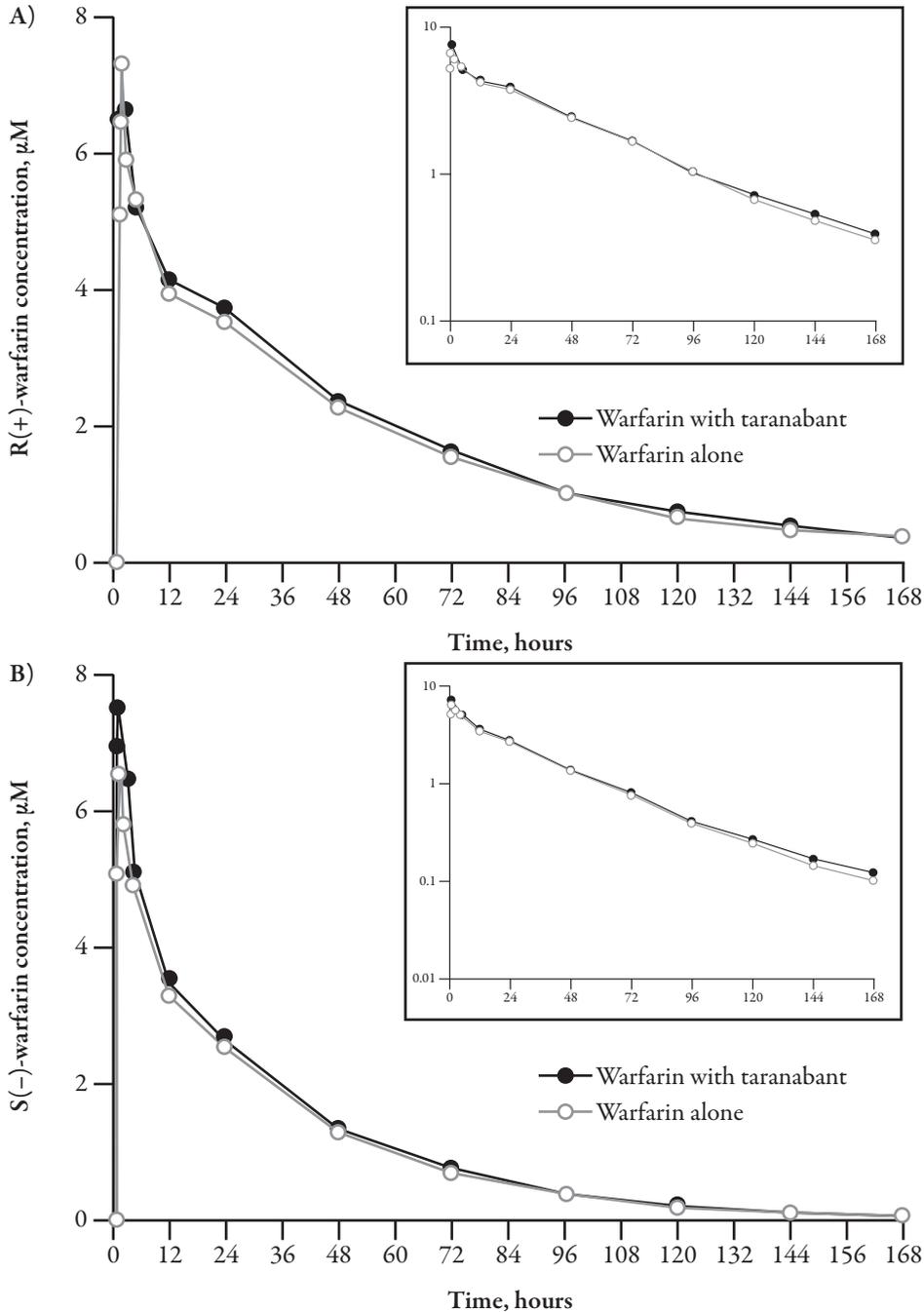
#Expressed as harmonic mean (jackknife SD) for apparent t_{1/2}.

§Hodges-Lehmann estimate of median difference with distribution free CI for T_{max}.

Apparent t_{1/2}=apparent terminal half-life; AUC_{0-∞}=area under the plasma concentration curve from zero to infinity; CI=confidence interval; C_{max}=maximum plasma concentration;

GMR=geometric mean ratio; NC=not calculated; T_{max}=time to maximum plasma concentration.

Figure 2. Mean plasma concentration profiles for R(+)-warfarin and S(-)-warfarin following a single 30 mg oral dose of warfarin 30 mg administered in the absence (Treatment A) and presence (Treatment B) of steady-state taranabant 6 mg. Data are plotted as mean (μM) plasma levels up to 168 hours postdose. (Figure inset: semi-log plot.)



The $AUC_{0-\infty}$ (primary endpoint) and C_{max} (secondary endpoint) of S(-)- and R(+)-warfarin were used to compare the pharmacokinetics of warfarin in the presence and absence of taranabant 6 mg. The GMRs (warfarin+taranabant/warfarin; 90% CI) for $AUC_{0-\infty}$ of S(-)- and R(+)-warfarin were 1.10 (90% CI: 1.03, 1.18) and 1.06 (90% CI: 1.00, 1.13), respectively (Table 2). The 90% CIs for $AUC_{0-\infty}$ GMRs of S(-)- and R(+)-warfarin all fell within the predetermined comparability bounds of 0.80 and 1.25, thus supporting the primary study hypothesis.

The C_{max} values for S(-)- and R(+)-warfarin were slightly increased in the presence of steady-state taranabant 6 mg. The GMRs (warfarin+taranabant/warfarin) for C_{max} of S(-)- and R(+)-warfarin were 1.16 (90% CI: 1.05, 1.28) and 1.17 (90% CI: 1.07, 1.29), respectively (Table 2). The upper bound of

the 90% CIs for both enantiomers extended beyond the predetermined upper comparability bound of 1.25. These findings did not support the secondary study hypothesis.

Pharmacodynamics

Summary statistics for the PT/INR pharmacodynamic endpoints following administration of single-dose warfarin 30 mg with and without steady-state taranabant 6 mg are shown in Table 3. Multiple-dose taranabant did not appear to alter the anticoagulant effect of single-dose warfarin. The GMR (warfarin+taranabant/warfarin) for the INR $AUC_{0-168\text{hours}}$ was 0.99 with corresponding 90% CI of 0.94 and 1.05. The GMR (warfarin+taranabant/warfarin) for the INR_{max} was 0.97 with corresponding 90% CI of 0.89 and 1.06.

Table 3. Pharmacodynamic parameters following administration of single-dose warfarin 30 mg alone (Treatment A) or in combination with multiple-dose taranabant 6 mg (Treatment B) in healthy subjects.

Pharmacodynamic parameter	<i>n</i>	Least-squares geometric mean (95% CI)†			<i>P</i> value
		Warfarin alone (Treatment A)	Coadministered warfarin+taranabant (Treatment B)	Least-squares GMR (90% CI)‡	
INR $AUC_{0-168\text{hours}}$	11	266.7 (226.9, 313.5)	265.2 (225.6, 311.7)	0.99 (0.94, 1.05)	0.8532
INR _{max}	11	2.6 (2.0, 3.3)	2.5 (1.9, 3.2)	0.97 (0.89, 1.06)	0.5525

P value is for testing if GMR=1.00. *P* value of <0.05 indicates the true GMR is statistically different from 1.00 at the significance level of 0.05.

†Expressed as least-squares geometric mean (95% CI) for INR $AUC_{0-168\text{hours}}$ and INR_{max}.

‡GMR for warfarin+taranabant/warfarin alone.

CI=confidence interval; GMR=geometric mean ratio; INR=prothrombin time international normalized ratio; INR $AUC_{0-168\text{hours}}$ =area under the prothrombin time international normalized ratio curve from 0 to 168 hours on day 21; INR_{max}=average maximum observed prothrombin time international normalized ratio.

Safety and Tolerability

Of the 10 clinical adverse experiences reported by five subjects, eight adverse experiences were considered possibly or probably drug-related (ie, asthenia [two reports], abdominal pain, diarrhea [two reports], rash, blurred vision, and vomiting) and two (ie, abdominal pain, eye pain) were considered probably not drug-related by the study investigator. All adverse experiences occurred while subjects were on taranabant 6 mg. All clinical adverse events were transient in duration and considered mild in intensity by the study investigator. Gastrointestinal system-related adverse experiences (ie, vomiting, diarrhea, upper abdominal pain) were the most commonly reported drug-related clinical adverse experiences. There were no nervous system-related clinical adverse experiences in this study. No serious clinical adverse experiences and no laboratory adverse experiences were reported in this study. There were no clinically significant effects of taranabant 6 mg on blood chemistry tests (including alanine and aspartate aminotransferase), hematology parameters, vital signs, and ECG parameters.

DISCUSSION

This study evaluated the effects of steady-state taranabant 6 mg (for 21 consecutive days), an orally active, highly selective, and potent CB1R inverse agonist,^{8,9} on the pharmacokinetics and pharmacodynamics of single-dose warfarin 30 mg. In this study, the pharmacokinetic ($AUC_{0-\infty}$, C_{max} , T_{max} , and $t_{1/2}$ of S[-] and

R[+]-warfarin) and pharmacodynamic parameters (INR $AUC_{0-168\text{hours}}$ and INR_{max}) of warfarin were monitored for up to 168 hours postdose to accommodate the long half-life of both warfarin enantiomers.

The results of this study showed that multiple-dose administration of taranabant 6 mg for 21 days does not alter the single-dose plasma pharmacokinetics of warfarin 30 mg as measured by $AUC_{0-\infty}$ of R(+)- and S(-)-warfarin enantiomers. The 90% CIs for the $AUC_{0-\infty}$ GMRs (warfarin+taranabant/warfarin) of R(+)- and S(-)-warfarin fell entirely within the predetermined comparability bounds of 0.80 and 1.25, thus supporting the primary study hypothesis. There was a slight but not a clinically important increase in C_{max} for each warfarin enantiomer following coadministration with warfarin. The upper bounds of the 90% CIs for the C_{max} GMRs of R(+)- and S(-)-warfarin (1.29 and 1.28, respectively) fell slightly outside the prespecified upper bound of 1.25. Furthermore, no meaningful differences in T_{max} and apparent $t_{1/2}$ were observed between the two treatments. Since the total exposure to S(-)- and R(+)-warfarin is unchanged during coadministration of taranabant and warfarin, no clinically meaningful effects on blood coagulation are expected. Nevertheless, any change in a drug therapy regimen where warfarin is being dosed warrants appropriate laboratory monitoring.

As a secondary endpoint this study also evaluated the effect of steady-state taranabant on the pharmacodynamics of single-dose warfarin as assessed by INR,

a biomarker of the anticoagulant effect of warfarin. The GMRs of $\text{INR AUC}_{0-168\text{hours}}$ and INR_{max} were close to unity (0.99 and 0.97, respectively). These findings are consistent with the expectation that slight increases in plasma levels of R(+)- and S(-)-warfarin (ie, C_{max}) do not lead to clinically meaningful effects on the anticoagulant efficacy of warfarin.

Concomitant administration of taranabant and warfarin was generally well tolerated in this population of healthy subjects. There were no instances of clinically significant bleeding or unusual changes in INR with either treatment. No subjects discontinued from this study due to adverse experiences. There were no clinically significant effects of taranabant 6 mg on blood chemistry tests, hematology parameters, vital signs, or ECG parameters. Taranabant was associated with a greater incidence of gastrointestinal-related adverse experiences compared with warfarin alone. Overall, clinical adverse experiences associated with taranabant were generally mild, transient, and self-limited in nature.

A notable caveat of this study is that the pharmacokinetics and pharmacodynamics of R(+)- and S(-)-warfarin were assessed following the administration of only a single dose of warfarin. Although the administration of single-dose warfarin 30 mg does not produce a stable anticoagulant effect in vivo, it does sufficiently raise the INR value to enable the detection of clinically meaningful pharmacodynamic interactions.²²⁻²⁴ In the present study, the mean INR_{max} attained with a single 30 mg dose of warfarin in the absence of taranabant was 2.6, which is within the clinically

relevant range normally used with anticoagulant therapy.^{11,13} Several published studies have successfully employed a similar single-dose warfarin/multiple-dose drug study design as a means to probe for possible warfarin-drug interactions.^{22,23,25,26} Schwartz et al. demonstrated that the single-dose model is predictive of the results obtained from a multiple-dose design.²⁷ This single-dose study design paradigm facilitates the investigation of possible interactions while mitigating the safety risks associated with exposing healthy subjects to multiple doses of warfarin. Other studies showing no drug-drug interaction with single-dose warfarin have also confirmed the lack of drug-drug interactions following chronic administration in clinical practice.^{23,24,28}

The results of the present study show that steady-state dosing with taranabant 6 mg, an orally active, highly selective, potent CB1R inverse agonist, does not affect systemic exposure (ie, $\text{AUC}_{0-\infty}$) to R(+)- or S(-)-warfarin, or the anticoagulant effect of warfarin. Slight increases in C_{max} of R(+)- and S(-)-warfarin were observed in the presence of taranabant, but these changes are not likely to be clinically meaningful considering the lack of effect on INR pharmacodynamics. Coadministration of multiple-dose taranabant with a single oral dose of warfarin was generally well-tolerated in this population of healthy male and female subjects. These results suggest that no dosage adjustment of warfarin is required when these drugs are concomitantly prescribed in clinical practice, but standard monitoring of PT should be continued.

A limitation of this study is that all patients enrolled were deemed Hispanic, although the protocol did not exclude patients from other ethnic backgrounds. This group was highly mixed with respect to origin and their Hispanic origin was identified by last name only and therefore does not reflect a pure origin. Hispanics are primarily Caucasian in origin by definition. Nevertheless, the results of this study may not be extrapolated to a wider non-Hispanic population.

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Disclosures and Conflicts of Interest

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