ODANACATIB DOES NOT INFLUENCE THE SINGLE DOSE PHARMACOKINETICS AND PHARMACODYNAMICS OF WARFARIN

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ABSTRACT

Background
Warfarin is an anticoagulant with a narrow therapeutic index that is involved in a number of drug-drug interactions.

Objectives
This study evaluates the potential effect of odanacatib (a cathepsin K inhibitor in development for the treatment of osteoporosis) on the pharmacokinetics and pharmacodynamics of warfarin.

Methods
In a randomized, open-label, two-period fixed-sequence design, 13 healthy, postmenopausal female subjects received two different treatments (Treatment A: a single dose of 30 mg warfarin; Treatment B: 3 once-weekly doses of 50 mg odanacatib with 30 mg warfarin co-administered with the last dose). Warfarin R(+) and S(-) enantiomer concentrations and prothrombin time were measured at pre-dose and at specified time points over 168 hours in each treatment period. Statistical analysis was performed using linear mixed effects model.

Results
Odanacatib was generally well tolerated when co-administered with warfarin in this study. The GMRs (95% confidence intervals [CI]) for plasma $AUC_{0-\infty}$ of warfarin+odanacatib/warfarin alone were 0.99 (0.94, 1.03) for warfarin R(+) and 1.00 (0.97, 1.03) for warfarin S(-), consistent with a lack of interaction between odanacatib and warfarin; results for C_{max}, T_{max}, and terminal $t_{½}$ provided also demonstrated no interaction. The GMR (warfarin + odancacatib/warfarin alone) and 95% CI for the statistical comparison of INR $AUC_{(0–168\ hr)}$ was 1.01 (0.98, 1.04).

Conclusions
The single dose pharmacokinetics and pharmacodynamics of orally administered warfarin were not meaningfully affected by multiple dose administration of odanacatib, indicating that odanacatib is not a clinically important inhibitor of CYPs 2C9, 3A4, 2C19, or 1A2.

Key Words: *Odanacatib, warfarin, CYP2C9, CYP3A4, CYP2C19, CYP1A2*

Odanacatib is a novel cathepsin K (Cat K) inhibitor being developed for the treatment of osteoporosis, a condition characterized by excess bone loss and fractures. Cat K is primarily responsible for bone matrix degradation by osteoclasts.[1] Following treatment with 50 mg odanacatib once weekly in postmenopausal women with osteoporosis, increased bone mineral

density (BMD) has been observed both at the lumbar spine and total hip.[2,3] Because of the large population of patients who may potentially benefit from treatment with odanacatib, testing for drug-drug interactions is clinically important. Warfarin is a medication used in a variety of conditions requiring anticoagulation such as cardiac arrhythmias, thrombosis, and myocardial infarction.[4,5] It is a highly protein bound drug (~99%) that is administered as a racemic mixture of R and S enantiomers. The S(-) enantiomer exhibits 5 – 6 times greater anticoagulant potency versus R(+) warfarin but a shorter plasma half-life of 32 hours compared with 43 hours, respectively.[6]

Drug-drug interactions with warfarin are common and can either increase or decrease anti-thrombotic efficacy, as measured by prothrombin time adjusted to the standardized parameter of the International Normalized Ration (INR).[7]

The metabolism of warfarin is relevant for evaluating the potential for drug interactions. S(-) warfarin is metabolized by the CYP2C9 isoenzyme while the R(+) warfarin is principally metabolized by CYPs 3A4, 2C19, and 1A2.[8,9,10,11] Assessing the potential for a warfarin interaction with novel agents during development is needed in the setting of likely co-administration to mitigate the risk of enhanced or possibly reduced warfarin anticoagulant efficacy. Enhanced efficacy could potentiate bleeding risk, while suboptimal efficacy is not protective from thrombotic complications. In human microsomal studies, the IC50 values against CYP1A2-, CYP2C9-, CYP2C19-, and CYP3A4-mediated reactions were all > 100 μM for odanacatib (data on file). Therefore, an interaction between warfarin and odanacatib is not anticipated.

The purpose of this study was to determine the effect of 50 mg odanacatib, the proposed clinical dose, on the plasma pharmacokinetics of warfarin (e.g., $AUC_{0-\infty}$, C_{max}, T_{max}, and apparent terminal $t_{1/2}$ for the R(+) and S(-) warfarin enantiomers) following co-administration of a single dose of warfarin to healthy postmenopausal female subjects. The safety and tolerability of concomitant administration of odanacatib and warfarin was also evaluated. Additionally, we evaluated the effect of odanacatib under steady state conditions on the pharmacodynamics of warfarin as assessed by the INR for PT following single-dose warfarin administration.

METHODS

This study (sponsor protocol # 025) was conducted from April 23, 2007 to June 5, 2007. The protocol for this study was reviewed and approved by Aspire Institutional Review Board, LLC and all patients provided informed consent prior to study conduct. This study was conducted following principles of Good Clinical Practice.

Patients

In order to be included in this study, subjects were healthy, nonsmoking, postmenopausal between 45 and 75 years of age, with a body mass index of ≤ 33 kg/m^2, and who were judged to be in good health based on medical history, physical examination, and laboratory safety tests.

Due to the risk of confounding the results of pharmacokinetic assessments, subjects refrained from grapefruit and grapefruit juice 14 days prior to the dosing and until the poststudy visit. Subjects were also instructed to limit leafy green vegetables for 2 weeks prior to the study due to the effect of vitamin K on INR values. Caffeinated beverages were stopped 24 hours prior to and after drug administration during each treatment period and 12 hours before prestudy and poststudy visits.

Study Design

This study was an open-label, 2-period, fixed-sequence study to determine the effect of odanacatib (at steady state) on the plasma concentrations of warfarin R(+) and S(-) enantiomers following a single dose of warfarin. Warfarin dosing in Period 1 was included to obtain pharmacokinetic data with warfarin alone; warfarin dosing in Period 2 was included to evaluate the victim potential of warfarin by measuring pharmacokinetic data at presumed steady state for odanacatib. Thirteen (13) healthy postmenopausal female subjects received a single oral dose of 30-mg warfarin on Day 1 of Period 1 followed by 3 once-weekly oral doses of 50 mg odanacatib administered with a high-fat breakfast

(Period 2, Days -14, -7, and 1). On Day 1 of Period 2, at presumed odanacatib steady state, odanacatib was co-administered with a single oral dose of 30 mg warfarin. Odanacatib typically has an apparent terminal half-life of approximately 70-80 hours. Plasma concentrations are anticipated to reach 90% of steady state after 3.3 half-lives, or roughly 230 hours (9.6 days). In this study, odanacatib was administered for 336 hours (14 days) (approximately 4.8 half-lives) prior to co-administration with warfarin (i.e., at presumed steady state). There was a minimum of 14 days from the last dose in Period 1 to the first dose of Period 2. Administration of all study drugs was witnessed. Blood samples for determination of warfarin R(+) and S(-) enantiomer concentrations and for prothrombin time (measured as PT and INR values in duplicate) were collected at pre-dose and at 0.5, 1, 2, 4, 12, 24, 48, 72, 96, 120, 144, and 168 hours following the warfarin dose in each treatment period. In Period 2, odanacatib blood samples were obtained at pre-dose and at specific time points over 168 hours following the first day of odanacatib dose administration (Period 2, Day -14) and pre-dose on Days -7 and 1 for determination of odanacatib steady-state plasma concentrations.

Pharmacokinetic Parameters

The profile of PT (measured as PT and INR values in duplicate) was measured predose and at 0.5, 1, 2, 4, 12, 24, 48, 72, 96, 120, 144, and 168 hours post warfarin dose in both treatment periods and poststudy; Area under the concentration-time curve to 168 hours ($AUC_{0\text{-}168\ hr}$) and INR_{max} were determined. The pharmacokinetics of warfarin enantiomers [R(+) and S(-)] were investigated after concomitant administration of a single 30 mg dose of warfarin with multiple 50 mg doses of odanacatib and after administration of 30 mg warfarin alone.

The following pharmacokinetic parameters were evaluated for both warfarin R(+) and warfarin S(-): Area under the concentration-time curve to infinity ($AUC_{0\text{-}\infty}$) (µg*hr/mL), C_{max} (µg/mL), T_{max} (hr), and apparent terminal $t_{1/2}$ (hr). $AUC_{0\text{-}\infty}$ was calculated as $AUC_{0\text{-}t} + C_t/\lambda_Z$ where: $AUC_{0\text{-}t}$ is the area under the concentration-time curve from hour 0 to the last measurable concentration estimated by the linear up/log down method, C_t is the last measurable concentration in plasma, and λ_z is the terminal phase rate constant estimated using log linear regression during the terminal elimination phase. The number of points used in λ_z calculation was determined by visual inspection of the data describing the terminal phase. $AUC_{0\text{-}\infty}$ values were not calculated for odanacatib in this study because a 168 hour concentration profile is insufficient for accurate estimate of the terminal phase rate constant for this compound. $AUC_{0\text{-}168\ hr}$ was calculated by the linear up/log down method. C_{max} was the maximum observed concentration in plasma over the complete profile and T_{max} was the time to maximum concentration over the complete profile. Apparent terminal $t_{1/2}$ was calculated using the formula $\ln(2)/\lambda$ (half-life values were not calculated for odanacatib in this study because a 168 hour concentration profile is insufficient for accurate estimate of the terminal phase rate constant for this compound). Plasma concentrations of warfarin enantiomers were determined by Advion BioServices, Inc., using validated turbo ion spray liquid chromatographic/tandem mass spectrometric (LC/MS/MS) methods. The lower limit of quantitation for both R(+)- and S(-)-warfarin was 10 ng/mL and the upper limit of quantitation was 2500 ng/mL.

Plasma samples for determination of odanacatib plasma concentrations were also obtained at selected time points over 168 hours post initial odanacatib dose. Pharmacokinetic parameters evaluated for odanacatib included $AUC_{0\text{-}168hr}$, C_{168hr}, $C_{max,overall}$, $T_{max,overall}$, $C_{max,day1}$, and $T_{max,day1}$. Plasma samples collected for odanacatib assay were analyzed by the Covance Bioanalytical Services, LLC (Indianapolis, Indiana). The analytical method for the determination of odanacatib used liquid-liquid extraction for analyte isolation followed by HPLC-MS/MS detection. The lower limit of reliable quantification (LLOQ) was 0.5 ng/mL (1 nM) and the linear calibration range was 0.5 to 500 ng/mL.

Safety

Safety and tolerability were assessed by measurement of vital signs (heart rate [HR], blood pressure [BP], respiratory rate [RR], and oral temperature), physical examinations, laboratory safety tests (hematology, chemistry, urinalysis, and stool occult blood test), and 12-lead electrocardiograms (ECG). Adverse experiences occurring during the course of the study and during the follow up period were evaluated by the investigator who determined their intensity, seriousness, and relationship to study drug.

Statistical Analysis

The primary hypothesis of this study was that multiple dose administration of odanacatib would not substantially influence the single dose pharmacokinetics of oral warfarin. That is, the true geometric mean ratios (GMRs) (warfarin + odanacatib/warfarin alone) for the plasma $AUC_{0-\infty}$ of warfarin enantiomers [R(+) and S(-)] would be contained in the interval (0.80, 1.25).

The secondary hypothesis was that dose administration of odanacatib would not substantially influence the single dose pharmacokinetics of oral warfarin. That is, the true GMRs (warfarin + odanacatib/warfarin alone) for the plasma C_{max} of warfarin enantiomers [R(+) and S(-)] are contained in the interval (0.80, 1.25).

The variance estimates for warfarin R(+) and S(-) $AUC_{0-\infty}$ and C_{max} were obtained from studies investigating the effects of various therapeutic agents on the single dose pharmacokinetics of warfarin. The pooled estimates for the within-subject standard deviation (SD) for warfarin R(+) and S(-) $AUC_{0-\infty}$ on the log scale are 0.076 and 0.081 (log μg•hr/mL), respectively. The pooled estimates for the within-subject SD for warfarin R(+) and S(-) C_{max} on the log scale are 0.088 and 0.123 (log μg/mL), respectively. The hypotheses evaluated in this study assumed a sample size of 12 subjects in a fixed sequence design and a type I error rate of α=0.05. The probability that the overall primary hypothesis will be supported is approximately 98%, given that the true GMRs are 1.00 for both primary endpoints.

A linear mixed-effect model was used to evaluate the hypotheses. The model included factors for subject (random effect) and treatment (fixed effect). The separate warfarin enantiomers [R(+) and S(-)] $AUC_{0-\infty}$ and C_{max} values were analyzed via the model after transformation to the natural log scale. Ninety percent confidence intervals (CIs) were constructed for GMRs (warfarin + odanacatib/warfarin alone) for both warfarin R(+) and S(-) $AUC_{0-\infty}$ and C_{max} from the model after back-transformation. The conclusion that co-administration of a single dose of warfarin with odanacatib does not influence $AUC_{0-\infty}$ of warfarin would be supported if both 90% CIs for the R(+) and S(-) $AUC_{0-\infty}$ GMRs were contained within the interval (0.80, 1.25). The secondary hypothesis regarding warfarin R(+) and S(-) C_{max} was tested in a similar manner. T_{max} was summarized by treatment. Harmonic means and jack-knife standard deviations were provided for apparent terminal $t_{½}$, by treatment.

The same methodology as described above for pharmacokinetic analyses was used to explore the effect of multiple dose of odanacatib on INR $AUC_{0\text{-}168\ hr}$ and INR_{max} for prothrombin time. A log transformation was applied to INR $AUC_{0\text{-}168\ hr}$ and INR_{max} data. Summary statistics and 90% CIs for INR $AUC_{0\text{-}168\ hr}$ and INR_{max} GMRs (warfarin with odanacatib/warfarin alone) were provided.

RESULTS

Patient Demographics and Accounting

There were 13 postmenopausal female subjects were included in this study with an average age of 57 years (range from 49 to 67 years). The mean height of the subjects was 166.9 cm (range from 161.2 to 173.0 cm) and the mean weight was 71.6 kg (range from 54.8 to 82.1 kg). Of the 13 subjects, 9 were white and 4 were black. One subject discontinued (withdrew consent) following a single dose of warfarin administered alone in order to resume medication for a preexisting condition; 12 subjects completed the study.

Pharmacokinetic and Pharmacodynamic Parameters

The primary hypothesis was satisfied (i.e., the 90% confidence intervals of the geometric mean ratios

[warfarin + odanacatib/warfarin alone] of $AUC_{0-\infty}$ and C_{max} of R(+) and S(-) warfarin fell within the prespecified bounds (0.80, 1.25)]; thus, the results of this study demonstrate that, in these subjects, odanacatib did not have an influence on the single dose pharmacokinetics of oral warfarin. (Table 1) Figure 1 shows that mean exposures were consistent for both R(+) and S(-) enantiomers with and without odanacatib co-administration. (Table 1)

TABLE 1 Summary of Statistical Analysis Results of Warfarin Plasma Pharmacokinetics and Pharmacodynamics

		Warfarin + Odanacatib			Warfarin			Warfarin + Odanacatib/Warfarin	
Analyte	Parameter (units)	N	GM	95% CI	N	GM	95% CI	GMR	90% CI
Warfarin R(+)	$AUC_{0-\infty}$(μg*hr/mL)	12	115.2‡	(99.7, 133.3)‡	12	116.8‡	(101.0, 135.1)‡	0.99	(0.94, 1.03)
	C_{max} (μg/mL)	12	1.68‡	(1.53, 1.83)‡	13	1.78‡	(1.63, 1.95)‡	0.94	(0.90, 0.98)
	T_{max} (hr)	12	4.00§	(2.00, 12.00)§	13	4.00§	(2.00, 4.02)§		
	Apparent terminal $t_{1/2}$ (hr)	12	48.0‖	10.1‖	12	50.0‖	8.2‖		
Warfarin S(-)	$AUC_{0-\infty}$ (μg*hr/mL)	12	72.3‡	(60.3, 86.6)‡	12	72.5‡	(60.5, 86.9)‡	1.00	(0.97, 1.03)
	C_{max} (μg/mL)	12	1.63‡	(1.48, 1.79)‡	13	1.74‡	(1.58, 1.91)‡	0.94	(0.90, 0.98)
	T_{max} (hr)	12	4.00§	(1.00, 12.00)§	13	4.00§	(1.00, 4.02)§		
	Apparent terminal $t_{1/2}$ (hr)	12	35.7‖	6.7‖	12	35.2‖	6.4‖		
INR	$AUC_{0\text{-}168\ hr}$	12	230.1‡	(204.5, 258.8)‡	12	228.1‡	(202.7, 256.6)‡	1.01	(0.98, 1.04)
	INR_{max}	12	2.01‡	(1.63, 2.47)‡	13	2.04‡	(1.66, 2.50)‡	0.98	(0.92, 1.05)

GM = Geometric Mean. GMR = Geometric Mean Ratio. CI = Confidence Interval.

‡ Geometric mean and 95% CI computed from least squares estimates from linear mixed effect model performed on the natural-log transformed values.

§ Median (minimum, maximum) reported for T_{max}.

‖ Harmonic mean and jack-knife standard deviation reported for apparent terminal $t_{1/2}$.

FIG. 1 Mean Warfarin R(+) (Panel A) and Warfarin S(-) (Panel B) Plasma Concentration-Time Profiles Following Administration of a Single Dose of 30 mg Warfarin With or Without Concomitant Administration of Odanacatib to Healthy Postmenopausal Female Subjects Administered a High Fat Meal (Log-Linear Scale).

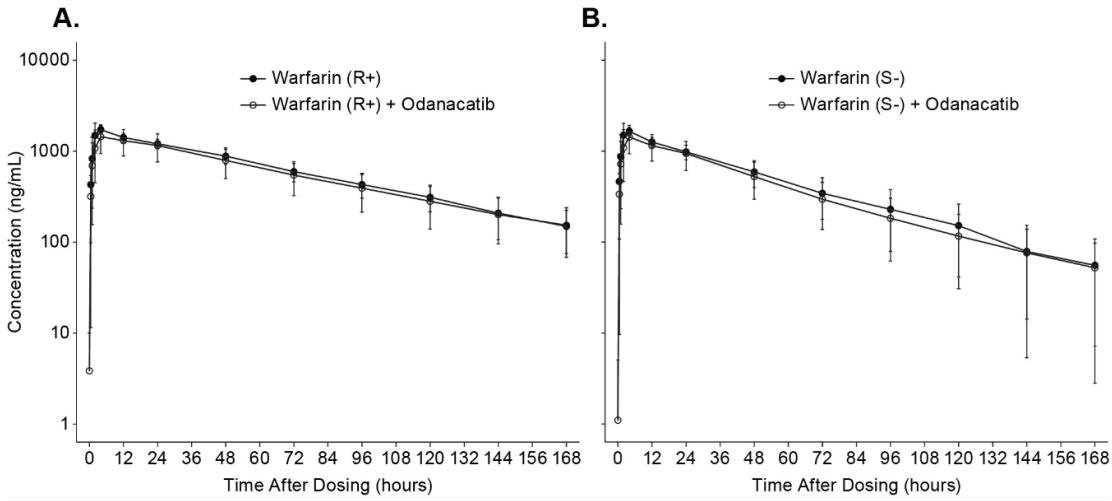
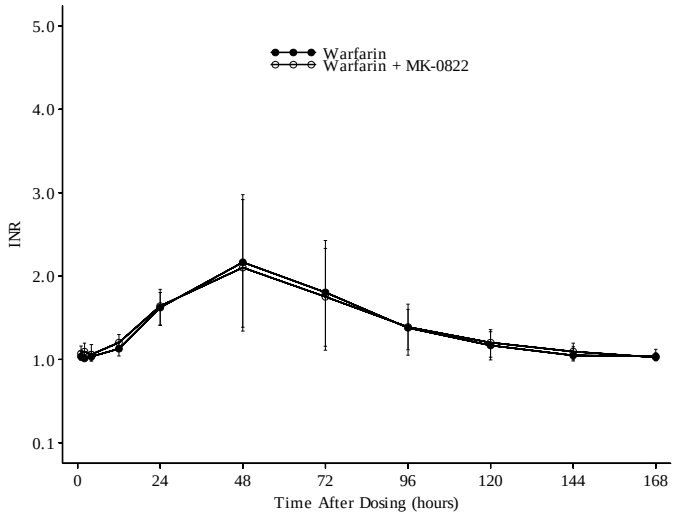


FIG. 2 Mean INR- time profiles following administration of a single dose of 30 mg warfarin with or without concomitant administration of odanacatib to healthy postmenopausal female subjects administered a high fat meal (log-linear scale). Error bars represent standard deviations.



Following concomitant administration of a single 30 mg dose of warfarin with multiple doses of odanacatib, the estimated GMR of INR $AUC_{0\text{-}168hr}$ and INR_{max} (90% CI) for co-

administration versus warfarin alone were respectively 1.01 (0.98, 1.04) and 0.98 (0.92, 1.05). (Table 1; Figure 2) The pharmacokinetics of odanacatib were also assessed to confirm that values are consistent with those observed in previous studies. Following a single oral dose administration of 50 mg odanacatib with a high fat meal, geometric mean values of 0.516 µM, 0.107 µM, and 46.1 µM·hr were observed for C_{max}, $C_{168\ hr}$, and $AUC_{0\text{-}168hr}$, respectively and the median $T_{max,}$ was 9.0 hours (Table 2).

Safety

No serious clinical adverse experiences were reported and no subject discontinued because of an adverse experience. Twenty (20) adverse experiences were reported by 9 subjects and all adverse experiences were rated mild in intensity. Adverse experiences reported with odanacatib + warfarin treatment were similar to those reported with warfarin alone and only 1 adverse experience was reported with odanacatib alone (Table 3). There were no consistent treatment-related changes in vital signs or ECG safety parameters. Additionally, there were no laboratory adverse experiences.

TABLE 2 Mean odanacatib pharmacokinetic parameters following single-dose administration of 50 mg odanacatib on Day-14, Period 2

Parameter	Geometric Mean (%CV) or Median
$AUC_{0\text{-}168hr}$ (µM*hr)	46.1 (27)
$C_{max,overall}$ (µM)	0.516 (19)
C_{168hr} (µM)	0.107 (57)
Median $T_{max,overall}$ (hr)	9.0

TABLE 3 Summary of AEs

	Treatment A (N = 13)		Treatment B			
			Odanacatib (N = 12)		Odanacatib + Warfarin (N = 12)	
	N	(%)	n	(%)	n	(%)
Subject/Subjects With One or More Adverse Experiences	5	(38.5%)	1	(8.3%)	7	(58.3%)
Flatulence	0	---	0	---	1	(8.3%)
Gingivitis	0	---	0	---	1	(8.3%)
Nausea	1	(7.7%)	0	---	2	(16.7%)
Rhinitis	1	(7.7%)	0	---	0	---
Contusion	1	(7.7%)	0	---	1	(8.3%)
Decreased appetite	0	---	0	---	1	(8.3%)
Musculoskeletal pain	1	(7.7%)	0	---	0	---
Dizziness	1	(7.7%)	0	---	1	(8.3%)
Headache	4	(30.8%)	1	(8.3%)	1	(8.3%)
Pharyngolaryngeal pain	0	---	0	---	1	(8.3%)
Rhinitis allergic	0	---	0	---	1	(8.3%)

Although a subject may have had two or more clinical adverse experiences, the subject is counted only once within a category.
The same subject may appear in different categories.
Treatment A=30 mg warfarin administered during Period 1.
Treatment B=50 mg odanacatib on Days -14 and -7, then 50 mg odanacatib + 30 mg warfarin on Day 1 administered during Period 2.

DISCUSSION

As odanacatib may be dosed in patients being treated with a narrow therapeutic index drug such as warfarin, understanding the effect of steady-state odanacatib, a novel cathepsin K inhibitor, on the pharmacokinetics and pharmacodynamics of warfarin is warranted. The results of this study fulfilled the primary hypothesis and demonstrated, in this study, that there was no clinically meaningful effect on the pharmacokinetics or pharmacodynamics of warfarin after concomitant administration of a single-dose of warfarin with oral odanacatib at projected steady state. These results are consistent with a lack of drug-drug interaction (DDI) potential for ODN as predicted by preclinical data (Data on file). Based on prior clinical studies, single-dose administration of 50 mg odanacatib with a high fat meal was anticipated to achieve a C_{max} of ~0.5 μM. In the present study, odanacatib was administered along with a high-fat meal to maximally assess the potential impact for an odanacatib-warfarin interaction.[12] The plasma levels of odanacatib were consistent with previous studies with an observed C_{max} geometric mean value of 0.516 μM. Notably, the C_{max} for odanacatib is > 100 fold lower than the IC50 against CYP2C9 and other CYPs, including CYP1A2, CYP2C1, and CYP3A4 suggesting that odanacatib may not have a significant inhibitory effect on these CYPs.

Odanacatib is in development for the treatment of osteoporosis. In postmenopausal women, odanacatib increases bone mineral density in a dose-dependent manner.[2,3,4] The present study enrolled postmenopausal women, the intended target population. Administration of warfarin requires careful monitoring given its narrow therapeutic index and propensity for frequent drug-drug interactions with untoward outcomes.[8,13,14,15] Dose adjustments are often required when an interaction is observed with warfarin to mitigate potential bleeding risks or ensure efficacious results. Given the lack of pharmacokinetic and pharmacodynamic interaction between odanacatib and warfarin observed in this study, these data would support the clinical use of odanacatib without the need for warfarin dose adjustment or additional therapeutic monitoring.

This study was conducted to also investigate the effect of ingesting a high fat meal, which increases odanacatib exposure up to ~2-fold; this did not negatively affect INR values.[12] No interaction was observed by odanacatib on warfarin PK and INR despite the ingestion of a high fat meal to maximally increase odanacatib concentration, and no serious or clinically concerning AEs were observed during this study. The most common AE was headache, observed primarily during the Period 1.

In summary, multiple-dose administration of odanacatib in the setting of a high fat meal to augment exposure, did not meaningfully alter the single dose pharmacokinetics of warfarin (either R(+) or S(-) enantiomers of warfarin) or pharmacodynamics of warfarin as assessed by prothrombin time INR in this study. Co-administration of odanacatib and warfarin to healthy postmenopausal women was generally well tolerated without noteworthy adverse experiences. These results suggest that no warfarin dose adjustment or additional INR monitoring would be required when used concomitantly with odanacatib and that odanacatib is not anticipated to be a clinically important inhibitor of CYPs 2C9, 3A4, 2C19, or 1A2. Moreover, these data indicate the low propensity for odanacatib to act as a perpetrator of drug-drug interaction at clinically relevant doses.

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