Multiple Doses of Odanacatib, a Novel Cathepsin K Inhibitor, Have No Influence on the Single-Dose Pharmacokinetics of Digoxin With Concomitant Administration

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Introduction

- Odanacatib is a novel selective cathepsin (cat) K inhibitor being developed for the treatment of osteoporosis.
- In order to evaluate drug-drug interactions involving clearance through P-glycoprotein (P-gp)-mediated activity, pharmacokinetic studies are often conducted using digoxin, a common medication that is cleared through passive glomerular filtration and P-glycoprotein (P-gp) mediated active tubular secretion in the kidney[1].
- Although odanacatib is not primarily eliminated through the kidney, there is a potential for an interaction since both odanacatib and digoxin are substrates of P-gp[2].

Purpose

- This study was conducted to determine the effect of multiple doses of 50 mg odanacatib on the plasma concentrations of immunoreactive digoxin following co-administration of a single dose of 0.5 mg digoxin and to assess safety and tolerability of concomitant administration of odanacatib and digoxin administered to healthy male and female subjects.

Methods

Subjects

- Subjects were healthy, nonsmoking males and females between the ages of 18 and 50 years with normal electrocardiograms (ECGs).
- All subjects had a BMI within the range of 18-32 kg/m^2.

Study Design

- This was an open-label, 2-period study to determine the effect of odanacatib on the plasma concentrations of immunoreactive digoxin (with a minimum washout period of 10 days between the last dose in the first period and the first dose in the second period).
  - Subjects received treatments in a fixed-sequence design: Treatment A followed by Treatment B. Treatment A consisted of a single oral dose of 0.5 mg digoxin on Day 1 of Period 1.
  - Treatment B consisted of 3 once-weekly oral doses of 50 mg odanacatib (i.e., dosing with odanacatib on Days -14, -7, and 1) with co-administration of a single oral dose of 0.5 mg digoxin on Day 1 of Period 2. Odanacatib has an apparent terminal half-life of approximately 70 hours.
- Odanacatib was administered for 336 hours (approximately 4.8 half-lives) prior to co-administration with digoxin (i.e., odanacatib and digoxin at presumed steady state).
- Blood samples (5 mL) for determination of immunoreactive digoxin concentrations were collected at predose and at specified time points for 120 hours following the digoxin dose in each treatment period.

Pharmacokinetic Parameters

- The calculated pharmacokinetic parameters included area under the concentration-time curve through 120 hours ($AUC_{0\text{-}120hr}$), maximum concentration of drug in the plasma (C_{max}), time to reach C_{max} (T_{max}), and apparent terminal half-life ($t_{½}$).

Safety

- Physical examinations, vital signs, 12-lead electrocardiograms (ECGs), and laboratory safety tests (blood chemistry, hematology, and urinalysis) were obtained at pre-specified time points. Subjects were monitored for adverse experiences (AEs) throughout the study.

Statistical Analysis

A linear mixed effects model appropriate for a 2-period fixed sequence study design was used to evaluate the hypothesis.

Results

Subject Demographics and Accounting

- There were 5 female and 7 male subjects included in this study with an average age of 29.3 years (range from 19 to 46 years) and an average BMI of 26 kg/m^2.
- All 12 subjects completed the study.

Pharmacokinetic Parameters

- Plasma concentrations of immunoreactive digoxin over time are shown in **Figure 1**. There was no difference in plasma concentration over time between digoxin alone and digoxin + odanacatib.
- **Table 1** shows a summary of pharmacokinetic parameters.
  - The estimated $AUC_{0\text{-}120hr}$ GMR (90% CI) for digoxin, when comparing co-administration of a single dose of 0.5 mg digoxin with 50 mg odanacatib following multiple once-weekly doses of odanacatib to 0.5 mg digoxin alone (digoxin + odanacatib/digoxin alone), was 0.95 (0.89, 1.01) (**Table 1**).
  - Both limits of the 90%CI were within the interval (0.80, 1.25); thus, the primary hypothesis, that multiple-dose administration of odanacatib does not substantially influence the single-dose pharmacokinetics of oral digoxin, was supported.

Figure 1: Arithmetic mean plasma immunoreactive digoxin concentration (ng/mL)-time (hr) for subjects administered single oral doses of 0.5 mg digoxin with and without co-administration of once-weekly oral doses of 50 mg odanacatib.

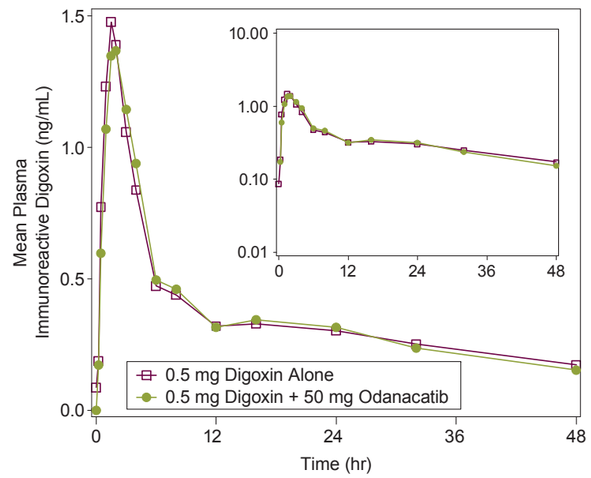

Table 1. Statistical Comparison of Digoxin Plasma Pharmacokinetic Parameters for Subjects Administered Single Oral Doses of 0.5 mg Digoxin With and Without Co-Administration of Once-Weekly Doses of 50 mg Odanacatib in Healthy Male and Female Subjects

Pharmacokinetic Parameter	Digoxin + Odanacatib		Digoxin Alone		Digoxin + Odanacatib/ Digoxin Alone	
	N	GM (95% CI)	N	GM (95% CI)	GMR (90% CI)	rMSE†
$AUC_{0\text{-}120hr}$‡ (ng•hr/mL)	12	19.78 (15.16, 25.79)	12	20.92 (16.04, 27.28)	0.95 (0.89, 1.01)	0.0869
C_{max}‡ (ng/mL)	12	1.61 (1.34, 1.93)	12	1.0 (1.42, 2.04)	0.95 (0.80, 1.12)	0.2281
T_{max}§ (hr)	12	1.75 (0.50, 3.00)	12	1.25 (0.50, 2.00)	0.25‖ (0.00, 0.75)‖	
Apparent terminal $t_{½}$¶ (hr)	11††	34.0 (9.8)	12			

†rMSE: Root mean square error on log-scale. When multiplied by 100, provides estimate of the pooled within-subject coefficient of variation.
‡Back-transformed least squares mean and confidence interval from mixed effects model performed on natural log-transformed values.
§Median (min, max) reported for T_{max}.
‖Median difference and CI from Hodges-Lehmann estimation reported for T_{max}.
¶Harmonic mean, jack-knife SD reported for $t_{½}$.
††For Subject AN 0010, following the administration of digoxin + odanacatib, the apparent terminal $t_{½}$ was not estimated due to absence of an apparent terminal phase.

Safety

- There were 20 clinical AEs during the treatment periods (7 following digoxin alone, 4 following odanacatib alone, and 9 reported following digoxin/odanacatib co-administration).
- AEs occurring with co-administration included nasal congestion, ear pain, headache, arthralgia, pharyngolaryngeal pain, diarrhea, and musculoskeletal pain; only nasal congestion (n=2) and headache (n=2) occurred in more than one subject.
- There were no serious AEs or AEs that led to discontinuation of study medication, and vital signs were normal.

Conclusions

- Concomitant administration of multiple doses of 50 mg odanacatib and single-dose 0.5 mg digoxin did not lead to a clinically important influence on the pharmacokinetics of digoxin, suggesting that odanacatib is not a clinically relevant inhibitor of P-gp.
- All treatments and concomitant administration were generally well tolerated.

References

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Disclosure

Authors Stoch, Witter, Hreniuk, Liu, Zajic, and Metha are employees of Merck.

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