Introduction

Purpose

- Odanacatib is a novel selective cathepsin 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. 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.

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/m².

Study Design

- This was an open-label, 2-period study to determine the effect of 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.

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/m².
- All 12 subjects completed the study.

Pharmacokinetic Parameters

- Plasma concentrations of immunoreactive digoxin over time are shown in Figure 1.

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

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Digoxin + Odanacatib</th>
<th>Digoxin Alone</th>
<th>Digoxin + Odanacatib/ Digoxin Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AUC₀⁻¹₂₀hr (ng·h/mL)</strong></td>
<td>12 19.78 (15.16, 25.79)</td>
<td>12 20.92 (18.04, 27.28)</td>
<td>0.95 (0.80, 1.12)</td>
</tr>
<tr>
<td><strong>C₀⁻¹₂₀hr (ng/mL)</strong></td>
<td>12 1.61 (1.34, 1.93)</td>
<td>12 1.0 (1.42, 2.04)</td>
<td>0.95 (0.80, 1.12)</td>
</tr>
<tr>
<td><strong>Tmax (hr)</strong></td>
<td>12 1.75 (0.50, 3.00)</td>
<td>12 1.25 (0.50, 2.00)</td>
<td>0.25 (0.00, 0.75)</td>
</tr>
<tr>
<td>Apparent terminal t₁/₂ (hr)</td>
<td>11†† 34.0 (9.8)</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

- All treatments and concomitant administration were generally well tolerated.

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


Acknowledgments

- Authors Stoch, Wittler, Henriuk, Liu, Zajic, and Mehta are employees of Merck.

Disclosure

- 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.

- Table 1 shows a 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 oral doses of 50 mg odanacatib.

- All 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.