BACKGROUND

• Paclitaxel is a widely used cytotoxic but is highly insoluble and poorly absorbed. The formulation vehicle cremophor adds toxicity.

• Oral paclitaxel avoids IV administration, hypersensitivity type reactions to Cremophor, and the need for steroid premedication.

• Oral paclitaxel improves patient convenience and may reduce dose-limiting toxicities such as neuropathy.

• Paclitaxel has poor oral bioavailability due to excretion by P-glycoprotein (P-gp) on intestinal cells. Oraxol is a combination of oral paclitaxel and HM30181A (INN: encequidar), a novel orally active, potent and specific inhibitor of P-gp with minimal systemic absorption. Based on prior studies, the bioavailability of 205 mg/m² oral paclitaxel + 15 mg encequidar 3 days per week was predicted to produce similar paclitaxel exposure as 80mg/m² IV paclitaxel.

• We report the results of a bio-equivalence study of Oraxol compared to IV paclitaxel 80mg/m².

METHODS

• This was an international, multicentre open-label, 2-stage study with a 2-treatment period, randomised crossover design.

• Eligible participants were adults with advanced cancer for whom weekly therapy with IV paclitaxel 80mg/m² over 1 hour is indicated.

• Primary objective was to confirm the bioequivalence (BE) of orally administered paclitaxel (with P-gp inhibitor encequidar) to that of IV paclitaxel.

• All patients received oral paclitaxel of 205 mg/m² plus 15mg encequidar both administered once daily for 3 consecutive days, followed at least one week later by IV paclitaxel 80mg/m², or the reverse order.

• PK blood samples were taken days 1-9 for oral paclitaxel and days 1-5 for IV paclitaxel 80 mg/m² over 1 hour.

• A sensitive LC-MS/MS assay was used for the determination of paclitaxel in human plasma. The PK data were analyzed by a noncompartmental method.

• BE of oral to IV paclitaxel dosing regimen was based on AUC. Geometric Mean Ratio (GMR) and 90%CI were estimated.

• Bioequivalence would be concluded if the 90% confidence intervals of AUCoral and AUCIV for paclitaxel were within 80.00% to 125.00%.

• Additional analyses included absolute bioavailability and the effect of Asian ethnicity on PK.

RESULTS

• 44 patients were randomized. 40 patients were enrolled. 35 patients completed both treatments and are included in PK analysis:

Table 1: Demographic Data and Baseline Characteristics (n=44):

| Age | Mean 60 years (Range 32-78) |
| Gender | Male: 14(35%) Female: 26 (65%) |
| Race | Caucasian: 29(73%) Asian:10 (25%) American Indian or Alaskan Native: 1 (2.5%) |
| ECOG | 0 (53%), 1 (47%) |
| Major Cancer Types | Breast cancer: 20 (50%) |
| Prior Treatment | Chemotherapy: 35 (87.5%), Surgery: 25 (62%), Radiation: 23(58%), Endocrine: 13 (35%), Biotherapy: 1(2%) |

• Figure 1 shows the mean plasma concentration time of Oraxol 205mg/m² daily x 3d and IV paclitaxel 80 mg/m² (N=35)

Table 2: GMR for AUC

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Geometric mean ratio (%)</th>
<th>90% Confidence interval</th>
<th>Intra subject CV %</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUCoral</td>
<td>89.50</td>
<td>83.89, 95.50</td>
<td>16.12</td>
</tr>
<tr>
<td>AUCIV</td>
<td>88.29</td>
<td>82.57, 94.41</td>
<td>16.68</td>
</tr>
</tbody>
</table>

• Table 2 shows the AUC parameter met bioequivalence. The results show the 90% confidence intervals for the parameters AUCoral and AUCIV for paclitaxel being (83.89,95.50) and (82.57,94.41), respectively.

• Table 3 shows Absolute Bioavailability Estimation of oral paclitaxel with encequidar (N=35), mean aBA is 11.8%.

• No apparent effect of Asian ethnicity on PK exposure and Absolute Bioavailability, Figure 2

• Treatment Preference: 30 (81%) subjects preferred oral paclitaxel with encequidar and 7(19%) subjects preferred IV paclitaxel. The reason reported most commonly for preferring oral paclitaxel with encequidar was that it is convenient and can be taken at home.

• Toxicity of Oraxol was limited, with principle toxicities of diarrhea, vomiting and fatigue. There were only 2 G3/4 TEAEs with Oraxol, and no treatment related deaths. We were only note one week of treatment was administered.

Figure 1: Plasma concentration v time of Oraxol and Paclitaxel 80mg/m²

Table 3: Descriptive Stats

<table>
<thead>
<tr>
<th>BSA</th>
<th>Mean</th>
<th>SD</th>
<th>CV%</th>
<th>Min</th>
<th>Max</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oraxol Dose (mg/m²)</td>
<td>617.1</td>
<td>2.5</td>
<td>0.40</td>
<td>613.6</td>
<td>627.3</td>
<td>616.7</td>
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<tr>
<td>Oraxol Dose (mg)</td>
<td>1,127</td>
<td>127</td>
<td>11</td>
<td>870</td>
<td>1,380</td>
<td>1,110</td>
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<tr>
<td>Paclitax IV Dose (mg)</td>
<td>80.1</td>
<td>1.5</td>
<td>1.89</td>
<td>76.5</td>
<td>83.5</td>
<td>80.0</td>
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<tr>
<td>Paclitax IV Dose (mg)</td>
<td>146</td>
<td>17</td>
<td>12</td>
<td>112</td>
<td>180</td>
<td>150</td>
</tr>
</tbody>
</table>

• Absolute Bioavailability (%) = 100*(AUCoral/Doseoral)/(AUCIV/DoseIV)

CONCLUSIONS

• Based on the area under the curve extrapolated to infinity (AUC0-∞), Oraxol 615 mg/m² is bioequivalent to the Reference Paclitaxel 80mg/m² IV treatment.

• At this dose level, the mean absolute bioavailability (aBA) is 11.8% for Oraxol.

• There is no apparent effect of Asian ethnicity on paclitaxel PK exposure following both iv and oral paclitaxel.

ACKNOWLEDGEMENTS

We are indebted to the patients who gave their valuable time to advance scientific discovery and aid future patients. We also thank their families who supported them throughout this trial and their cancer journey. We are grateful to Zentech staff, the Oncology Research Nurses & Admin at Southern DHB, Auckland DHB, Monash University, and CCDHB. This study was sponsored and funded by Athenex, Buffalo, NY.

REFERENCES


