477P - An international randomized cross-over bio-equivalence study of oral paclitaxel + HM30181A (Oraxol) compared with weekly intravenous (IV) paclitaxel 80mg/m^2 in advanced solid tumours

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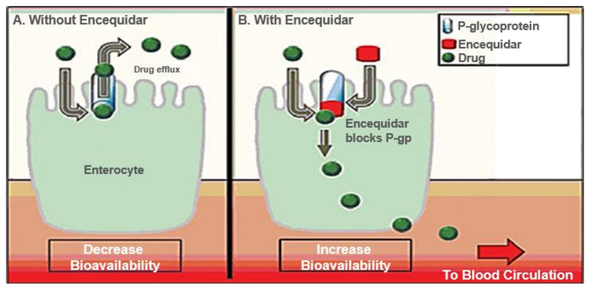
BACKGROUND

- 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/m^2 oral paclitaxel + 15 mg encequidar 3 days per week was predicted to produce similar paclitaxel exposure as 80mg/m^2 IV paclitaxel.



- We report the results of a bio-equivalence study of Oraxol compared to IV paclitaxel 80mg/m^2.

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/m^2 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/m^2 plus 15mg encequidar both administered once daily for 3 consecutive days, followed at least one week later by IV paclitaxel 80mg/m^2, or the reverse order.
- PK blood samples were taken days 1-9 for oral paclitaxel and days 1-5 for IV paclitaxel 80 mg/m^2 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 $AUC_{0-\infty}$ and AUC_{0-t} 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/m^2 daily x 3d and IV paclitaxel 80 mg/m^2 (N=35)
- **Table 2** shows the AUC parameter met bioequivalence. The results show the 90% confidence intervals for the parameters AUC0-∞ and AUC0-t 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 note only one week of treatment was administered.

Figure 1: Plasma concentration v time of Oraxol and Paclitaxel 80mg/m^2

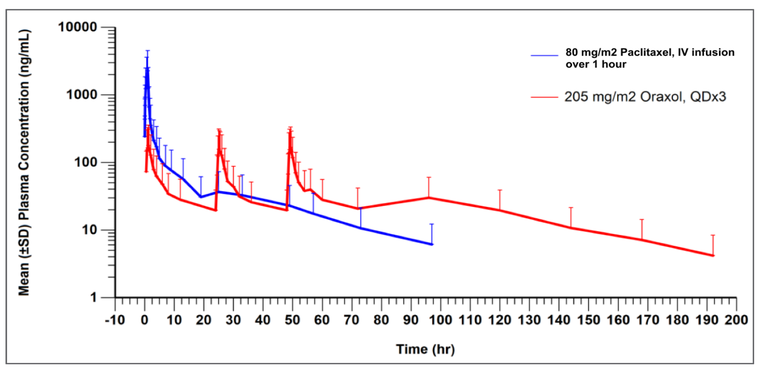


Table 2: GMR for AUC

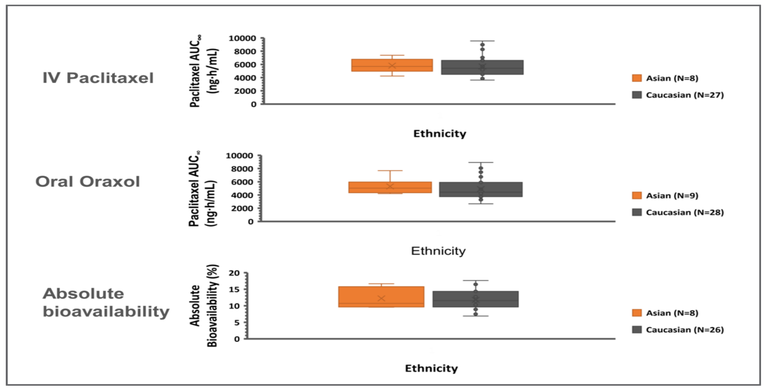
PK Parameter	Geometric mean ratio (%)	90% Confidence interval	Intra subject CV %
$AUC_{0-\infty}$	89.50	83.89, 95.50	16.12
AUC_{0-t}	88.29	82.57, 94.41	16.68

Table 3

Descriptive Stats	Mean	SD	CV%	Min	Max	Median
BSA	1.83	0.21	11.41	1.40	2.24	1.80
Oraxol Dose (mg/m^2)	617.1	2.5	0.40	613.6	627.3	616.7
Oraxol Dose (mg)	1,127	127	11	870	1,380	1,110
Paclitaxel IV Dose (mg/m^2)	80.1	1.5	1.89	76.5	85.3	80
Paclitaxel IV Dose (mg)	146	17	12	112	180	150
Absolute Bioavailability (%)[a]	11.8	2.7	23	7.1	17.1	11.2

[a]Absolute bioavailability (%) = 100*(AUC_{oral}/$Dose_{oral}$)/(AUC_{iv}/$Dose_{iv}$).

Figure 2: PK Parameters by ethnicity



CONCLUSIONS

- Based on the area under the curve extrapolated to infinity (AUC0-∞), Oraxol 615 mg/m^2 is bioequivalent to the Reference Paclitaxel 80mg/m^2 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

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