An open label, randomised cross-over bioavailability and extension study of Oral Paclitaxel and HM30181 (Oraxol) compared to weekly intravenous paclitaxel 80mg/m^2 in advanced solid tumours

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INTRODUCTION AND BACKGROUND

- Paclitaxel is a widely used cytotoxic but is highly insoluble and poorly absorbed
- The formulation vehicle cremophor contributes to hypersensitivity and peripheral neuropathy
- Paclitaxel is actively extruded back into the gut lumen from the mucosa by intestinal p-glycoprotein (Pgp)
- Oral paclitaxel would reduce IV access, avoid severe anaphylactic reactions to cremophor, potentially reduce peripheral neuropathy, and would offer cost savings and greater patient convenience
- There is a clinical need for an oral formulation of Paclitaxel
- Prior research with the p-gp inhibitors cyclosporin, ritonavir, elacridar could not achieve comparable exposure with oral compared to to IV paclitaxel

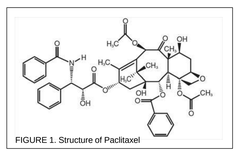

FIGURE 1. Structure of Paclitaxel

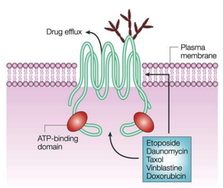

FIGURE 2. Pgp pump

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ORAXOL

- Oraxol (Athenex, Buffalo, NY) is a combination of oral paclitaxel together with HM30181, a novel, orally administered, non-absorbed specific inhibitor of intestinal Pgp.
- HM30181 is a potent inhibitor of intestinal Pgp with effects in healthy volunteers lasting for up to 15 days
- A prior study showed that paclitaxel 615mg/ m^2 in 2 divided doses could achieve AUC comparable to IV paclitaxel 80mg/m^2, but neared saturation over 2 days. We proposed a three-day regimen for further testing

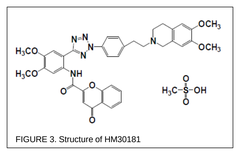
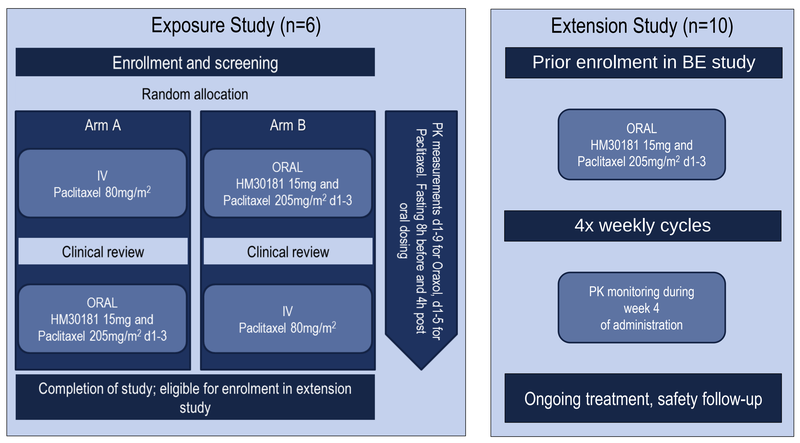


FIGURE 3. Structure of HM30181

- We conducted a pharmacokinetic study to compare exposure of Oraxol 205mg/m2 on days 1-3 repeated weekly to IV Paclitaxel 80mg/m^2, and an extension study to test comparability of PK at baseline and 4 weeks.

STUDY SCHEMA



Main inclusion and exclusion criteria

Advanced (incurable) solid tumours

Scheduled to receive Paclitaxel 80mg/m^2 i.v. weekly as monotherapy or in combination

Age >18, ECOG 0-1, life expectancy > 3 months

Haemoglobin >90g/L, Bilirubin <20umol/L; ALT< 3x upper limit normal, CrCl > 50ml/min by Cockroft and Gault formula

Willing to fast, and undergo confinement for PK blood sampling

No upper gastrointestinal surgery or conditions preventing absorption

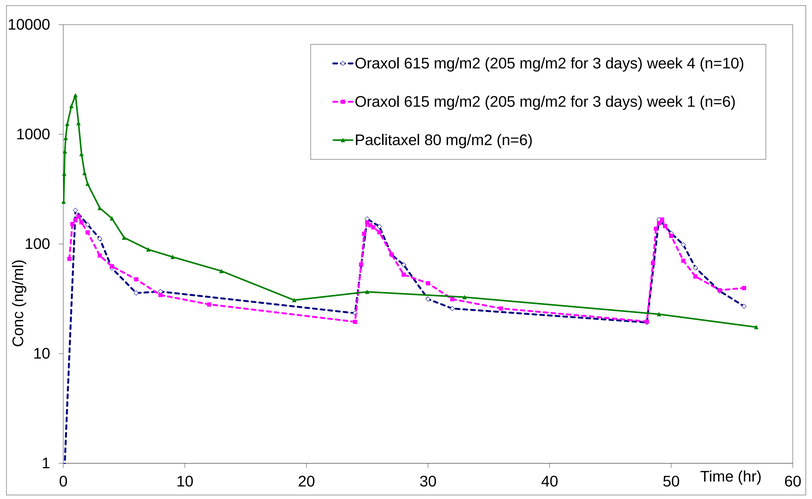
Willing to abstain from caffeine and alcohol

Prohibited meds: CYP 3A4, 2C8 inducers or inhibitors, P-gp inhibitors or inducers; critical p-gp substrates e.g. digoxin

RESULTS

- We report the results of the first scheduled interim analysis of a pharmacokinetic bioequivalence (exposure) study of Oraxol compared to IV paclitaxel, and the results of an extension study with repeat PK sampling after 4 weeks administration.
- Only the results from the first 6 patients in the exposure study are presented, as specified in the protocol
- Patient characteristics:
  - *Exposure study* site of primary tumour: breast (2), oesophagus, neuroendocrine small cell, colon, ovary
  - *Extension study* site of primary tumour: breast (6), colon, oesophagus, cholangiocarcinoma, ovary

	n	Median age, years (range)	Weight, kg (SD)	Height, m (SD)	BSA (SD)
Exposure study	6	61 (48-77)	81.02 (17.70)	1.70 (0.06)	1.93 (0.22)
Extension study	10	63.5 (48-77)	75.19 (13.89)	1.64 (0.11)	1.80 (0.20)



SUMMARY PHARMACOKINETIC DATA

	Paclitaxel 80mg/m^2 IV (n=6) Mean (SD)	Oraxol, Baseline (n=6) Mean (SD)	Oraxol Week 4 (n=10) Mean (SD)
$AUC_{0-\infty}$, (hr*ng/mL)	5652 (1013)	5078 (1723)	
Cmax (ng/mL)	2269.44 (227.11)	230.99 (133.84)	238.8 (86.11)
AUC_{0-56}		2493.4 (731.96)	2615.04 (707.14)
GMR (%, 90% CI)		87.09 (74.61-101.66)	
Intra-subject CV (%)		12.62	

There was one treatment related SAE (tachycardia) which resolved.

Treatment related toxicities were mostly GI and haematological, and manageable.

One patient remained on study > 1 year without neuropathy.

CONCLUSIONS AND FUTURE DIRECTIONS

Oraxol 205mg/m^2 PO d1-3 achieved paclitaxel AUC comparable to IV paclitaxel 80mg/m^2.

This schedule of Oraxol is within predicted range needed to demonstrate equivalent exposure to paclitaxel 80mg/m^2 IV.

4-week PK results show PK profile is not altered with repeated dosing.

A phase 3 study of Oraxol 205mg/m2 d1-3 compared to 3-weekly paclitaxel in patients with metastatic breast cancer is ongoing.

These findings suggest that Oraxol is an ideal drug candidate to replace IV paclitaxel

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