AN OPEN-LABEL, RANDOMIZED CROSS-OVER BIOAVAILABILITY STUDY OF ORAL PACLITAXEL AND HM30181A COMPARED WITH WEEKLY INTRAVENOUS (IV) PACLITAXEL IN PATIENTS WITH ADVANCED SOLID TUMOURS.

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DISCLOSURES

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No other disclosures.
BACKGROUND

Paclitaxel 175mg/m² q3w FDA-approved indication in breast cancer; 80mg/m² q1w improves PFS and OS in adjuvant breast Ca with less neutropenia, myalgia; more neuropathy¹

Oral agents may improve convenience, reduce health care utilisation, obviate need for CVADs, and remove cremophor-required premedication

Paclitaxel highly insoluble; actively extruded by gut localised permeability glycoprotein (p-gp). Undergoes extensive first pass metabolism

Prior research with Pgp inhibitors cyclosporin, ritonavir, elacridar could not achieve bioequivalence²

HM30181A Methane Sulfonate Monohydrate is a novel, minimaly-absorbed pgp inhibitor with no DLT seen in prior study, n=105.

Prior phase I study dosed at 270mg d1-2, 274mg/m² d1-2, 313mg/m² d1-2; saturation seen³; AUC approached that of paclitaxel 80mg/m². Selected 205mg/m² over 3 days for current dosing

KX-ORAX-002: study design

**Main inclusion and exclusion criteria**

**Advanced solid tumours**

- Scheduled to receive Paclitaxel 80mg/m² i.v. weekly
- Age >18, ECOG 0-1, life expectancy > 3 months
- HB>100, Bili <20; ALT<3x ULN, CrCl > 50ml/min
- Willing to fast, and undergo confinement for PK’s; no UGI surgery or conditions preventing absorption
- Prohibited meds: CYP 3A4, 2C8 inducers or inhibitors
- PGP inhibitors or inducers; critical PGP substrates e.g. digoxin

**Enrollment and screening**

**Random allocation**

**Arm A**

- IV Paclitaxel 80mg/m²

**Arm B**

- ORAL HM30181 15mg and Paclitaxel 205mg/m² d1-3

**Clinical review**

- PK measurements d1-3 for Oraxol, d1-5 for Paclitaxel. Fasting 8h before and 4h post oral dosing

**Completion of study; eligible for enrolment in extension study**

**Characteristics**

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Number of Patients</td>
<td>6</td>
</tr>
<tr>
<td>Age: mean (SD)</td>
<td>61 (12.76)</td>
</tr>
<tr>
<td>Gender</td>
<td>3 Males, 3 Females</td>
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<tr>
<td>BSA (m²): mean (SD)</td>
<td>1.9 (0.2)</td>
</tr>
<tr>
<td>Primary Cancer Diagnosis (n)</td>
<td>Breast Cancer (2), Esophageal (1), Ovarian (1), Prostate (1), Colon (1)</td>
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**Study Design**

- **Study Design**:
  - **Objectives**: Evaluate the safety and pharmacokinetics of Oraxol and Paclitaxel.
  - **Inclusion Criteria**:
    - Advanced solid tumours
    - Age >18, ECOG 0-1, life expectancy > 3 months
    - HB>100, Bili <20; ALT<3x ULN, CrCl > 50ml/min
    - Willing to fast, and undergo confinement for PK’s; no UGI surgery or conditions preventing absorption
    - Prohibited meds: CYP 3A4, 2C8 inducers or inhibitors
    - PGP inhibitors or inducers; critical PGP substrates e.g. digoxin
  - **Exclusion Criteria**:
    - Cannot be scheduled to receive Paclitaxel 80mg/m² i.v. weekly
    - Age <18, ECOG >1
    - Life expectancy < 3 months
    - HB<100, Bili >20; ALT>3x ULN, CrCl < 50ml/min
    - Cannot fast or confined for PK’s
    - Cannot undergo UGI surgery or conditions preventing absorption
    - Cannot use prohibited meds
    - Cannot use critical PGP substrates

- **Random Allocation**:
  - **Arm A**: IV Paclitaxel 80mg/m²
  - **Arm B**: ORAL HM30181 15mg and Paclitaxel 205mg/m² d1-3

- **Clinical Review**:
  - PK measurements d1-3 for Oraxol, d1-5 for Paclitaxel. Fasting 8h before and 4h post oral dosing

- **Completion of Study**:
  - Completion of study; eligible for enrolment in extension study
RESULTS: per-protocol interim analysis of first 6 patients

Interim PK results indicate that Oral Paclitaxel and HM30181A (Oraxol) can be dosed to achieve similar blood paclitaxel concentrations to IV paclitaxel in terms of AUC
INTERPRETATION

Oral dosing with paclitaxel is more convenient for patients and has many advantages. HM30181A 15mg and Oral Paclitaxel 205mg/m² on days 1-3 achieves similar AUC to IV paclitaxel 80mg/m².

No G3/4 toxicities were seen, and G1/2 toxicities were easily managed.

A total sample size of 30 subjects is required to demonstrate bioequivalence between Oraxol and IV paclitaxel (90% CI of the GMR is within the limits of 80% – 125%), with 80% power.¹

KX-ORAX-003 is ongoing to establish safety and tolerability with multiple day dosing.

This study demonstrates that Oral dosing is feasible and provides an ideal candidate to be tested to replace i.v. paclitaxel.

A randomised phase 3 study in metastatic breast cancer is underway comparing IV paclitaxel 175mg/m² q3w to weekly ORAL HM30181 and paclitaxel 205mg/m² (Oraxol) d1-3.

¹ Hauschke D J Pharmacokin Biopharm 1992; 20:557-561
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- Athenex staff

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