TPS1116

An Open-Label, Randomized, Multicenter, Phase 3 Registrational Study to Determine the Safety, Tolerability, and Tumor Response of Oral Paclitaxel and Encequidar (formerly HM30181A) and its Comparability to IV Paclitaxel in Patients With Metastatic Breast Cancer (MBC) (NCT02594371)

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BACKGROUND

- Paclitaxel is widely used in the management of a number of solid tumors, including breast cancer.
- IV administration is inconvenient, causes patient stress and discomfort, and is associated with serious toxicities and significant side effects.[1]
- The presence of Cremophor in the most widely used IV formulation of paclitaxel. is associated with hypersensitivity-type reactions that require pretreatment with corticosteroids and antihistamines. Cremophor may also contribute to paclitaxel-associated neuropathy.[2]
- Paclitaxel is a substrate for P-glycoprotein (P-gp), which is an ATP-dependent efflux pump that actively transports substrates from the intestinal epithelium back into the intestinal lumen.[3]
- Orally administered paclitaxel would obviate the need for IV infusion and pretreatment with high-dose corticosteroids and antihistamines, avoid the risk of hypersensitivity-type reactions, and provide greater patient convenience.
- It has been suggested that paclitaxel exposure (AUC) is related to efficacy while C_{max} is related to toxicity.[4-7] Therefore, oral therapy may be be better tolerated than IV therapy.
- Encequidar is an orally active, highly selective, and potent P-gp inhibitor with low systemic exposure. This study is designed to assess the safety, tolerability, and efficacy of oral paclitaxel and encequidar therapy versus IV paclitaxel in the treatment of patients with metastatic breast cancer.

ENCEQUIDAR

Figure 1. Encequidar: An Orally Active, Highly Selective, Potent, P-glycoprotein (P-gp) Inhibitor

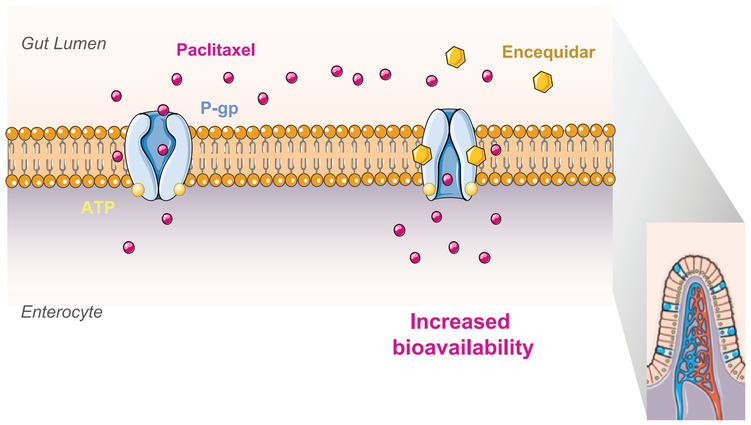
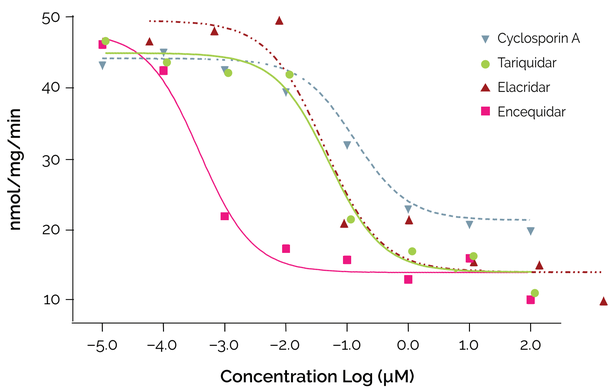


Figure 2. Comparative P-glycoprotein (P-gp) Inhibition Concentration



Inhibition concentration against P-gp transporter

	IC_{50} (nM)
Cyclosporin A	123.1
Tariquidar	44.4
Elacridar	4.9
Encequidar	**0.6**

Encequidar: In Vivo Activity—Favorable Safety and Toxicity Profile

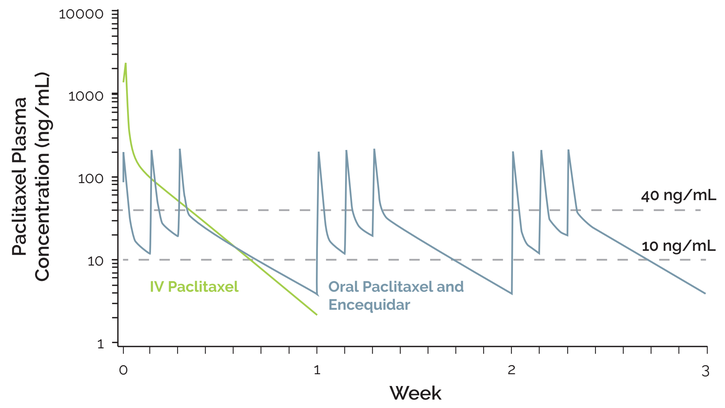
- **Pharmacokinetic (PK) studies in rats and dogs:** Encequidar is minimally absorbed and predominantly localized in the gastrointestinal tract.
- **Toxicology studies:** In rats, no mortalities, test article-related clinical signs, body weight changes, or gross necropsy with doses of up to 2000 mg/kg.

Encequidar: Phase 1 Clinical Trial

- 81 subjects received encequidar tablets up to 900 mg as a single dose, and 24 subjects received multiple doses of encequidar tablets from 60–360 mg per day for 5 days.
- Encequidar was well tolerated with no SAE, DLT, or MTD.

ORAL PACLITAXEL AND ENCEQUIDAR

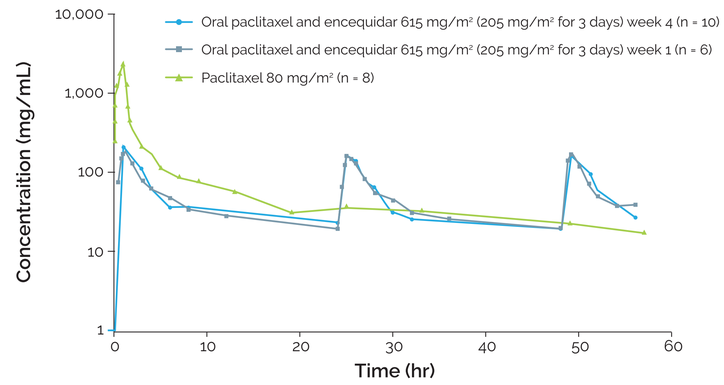
Figure 3. Oral Paclitaxel and Encequidar—A New Chemotherapy Paradigm



Bioavailability Study Comparing IV Paclitaxel to Oral Paclitaxel and Encequidar

- The results of the first scheduled interim analysis of a PK study of oral paclitaxel and encequidar compared with IV paclitaxel (80 mg/m²). Analysis of the preliminary PK suggest that oral paclitaxel and encequidar (205 mg/m² for 3 consecutive days, weekly), can acheive an AUC similar to IV paclitaxel (80 mg/m²), and has a C_{max} approximately 1/10 of IV paclitaxel.[8]

Figure 4. Pharmacokinetics of Oral Paclitaxel and Encequidar vs IV Paclitaxel



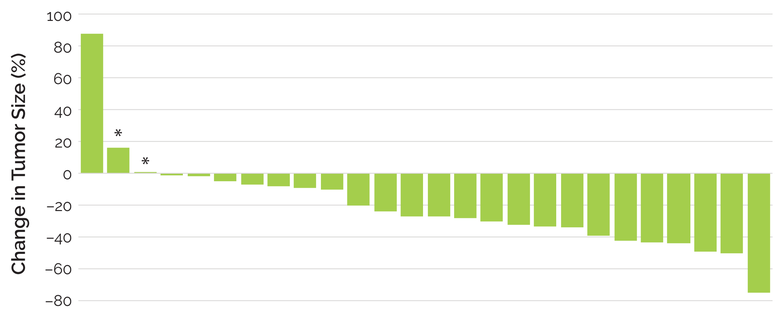
	Paclitaxel (n = 6) Mean (SD)	Oral Paclitaxel and Encequidar (n = 6) Mean (SD)
$AUC_{0-\infty}$ (hr*ng/mL)	5652 (1013)	5078 (1723)
C_{max} (ng/mL)	2269.44 (227.11)	230.99 (133.84)
AUC_{0-56}		2493.4 (731.96)
GMR (%; 90% CI)		87.09 (74.61-101.66)
Intra-subject CV (%)		12.62

$AUC_{0-\infty}$, area under the concentration-time curve from 0 to infinity; AUC, area under the concentration-time curve from time 0 to 56; CI, confidence interval; C_{max}, maximum concentration; CV, coefficient of variation; GMR, geometric mean ratio; SD, standard deviation.

Phase 2 Clinical Trial

- In a Phase 2, multicenter, single-arm, open-label study in patients with breast cancer (n = 28; 26 evaluable for tumor response) oral paclitaxel 205 mg/m² and encequidar 15 mg administered orally daily for 3 consecutive days and weekly for up to 16 weeks, showed encouraging clinical efficacy.[9]

Figure 5. Best Tumor Response



*Progressive disease due to new lesion

- Partial response: 11 patients (42.3%); stable disease: 12 patients (46.2%); progressive disease: 3 patients (11.5%); progression free after 16 weeks: 23 patients (88.5%)

PHASE 3 REGISTRATION STUDY

Primary Objectives

- To determine the safety, tolerability, and tumor response of oral paclitaxel and encequidar compared with IV paclitaxel
- To evaluate tumor response
  - Confirmed tumor response was evaluated according to RECIST v1.1
  - Confirmed response on 2 occasions according to a blinded central radiologist review

Secondary Objectives

- To evaluate progression-free survival (PFS) and overall survival (OS)

Patients and Dosing Regimen

- To date 402 patients have been randomized 2:1 (2 oral paclitaxel and encequidar: 1 IV paclitaxel) across 44 sites in Central and South America (Argentina = 15, Guatemala = 7, Chile = 6).

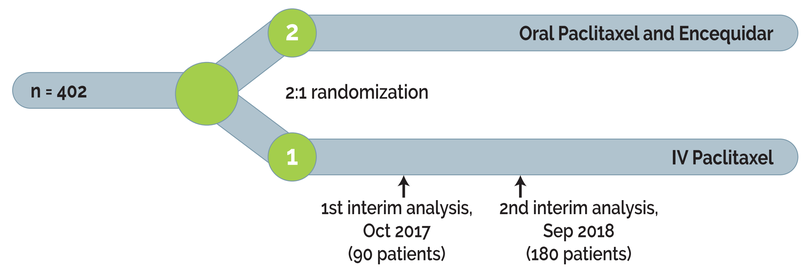
Key Inclusion Criteria	Key Exclusion Criteria
Adult female with histologically or cytologically confirmed metastatic breast cancer for whom treatment with IV paclitaxel monotherapy has been recommended by their oncologist	CNS metastasis
Must have measurable metastatic target lesion disease	Taking a medication known to be a strong P-gp inhibitor or inducer within 14 days of starting therapy
ECOG performance status of 0 or 1	Have not recovered to ≤grade 1 toxicity from previous anticancer treatments or previous investigational products
Adequate hematological status not requiring G-CSF. Adequate renal function (serum creatinine level <1.5 ULN) and hepatic function	

CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group G-CSF, granulocyte colony-stimulating factor; P-gp, P-glycoprotein; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; ULN, upper limit of normal.

Dosing Regimen

- Encequidar 15 mg followed by 205 mg/m² oral paclitaxel administered once daily for 3 consecutive days every week during Weeks 1 through 18 or 21 (encequidar is administered 1 hour before oral paclitaxel on all dosing days).
- IV paclitaxel 175 mg/m² (Taxol® or generic paclitaxel) as a 3-hour infusion every 3 weeks (Weeks 1, 4, 7, 10, 13, 16, and 19).
- Patients responding to either therapy can continue treatment.

Figure 6. Study Design



No corticosteroid or antihistamine premedication allowed for Oral Paclitaxel and Encequidar arm

PHASE 3 STUDY SUMMARY

- At the time of the second DSMB the study was not stopped for futility based on the endpoint of confirmed tumor response. The study is continuing to the final analysis.
- Enrollment to the study has been completed.
- Top-line results for confirmed response rate are expected to be available in 2019.

References

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