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.

Orally administered paclitaxel would obviate the need for IV infusion and pretreatment with high-dose corticosteroids and antiemetics, 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 Cmax is related to toxicity. Therefore, oral therapy may 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**

<table>
<thead>
<tr>
<th>P-gp Inhibitor</th>
<th>Inhibition Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporin A</td>
<td>123.1</td>
</tr>
<tr>
<td>Tarquidar</td>
<td>44.4</td>
</tr>
<tr>
<td>Elacridar</td>
<td>4.9</td>
</tr>
<tr>
<td>Encequidar</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Encequidar: In Vivo Activity—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 achieve an AUC similar to IV paclitaxel (80 mg/m²), and has a Cmax approximately 1/10 of IV paclitaxel.

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Oral Paclitaxel (n = 8)</th>
<th>IV Paclitaxel (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AUC</strong></td>
<td>259.44 (2271)</td>
<td>9078 (123)</td>
</tr>
<tr>
<td><strong>Cmax</strong></td>
<td>290.99 (133.54)</td>
<td>1753.4 (216)</td>
</tr>
<tr>
<td><strong>AUC/Cmax</strong></td>
<td>78.09 (74.61-101.68)</td>
<td>2493.4 (291.6)</td>
</tr>
</tbody>
</table>

#### Table: AUC and Cmax Comparison

<table>
<thead>
<tr>
<th>P-gp Inhibitor</th>
<th>AUC (hr ng/mL)</th>
<th>Cmax (ng/mL)</th>
<th>GMR (90% CI)</th>
<th>Intra-subject CV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporin A</td>
<td>125.1</td>
<td>290.99</td>
<td>78.09</td>
<td>12.62</td>
</tr>
<tr>
<td>Tarquidar</td>
<td>44.4</td>
<td>290.99</td>
<td>78.09</td>
<td>12.62</td>
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<td>0.6</td>
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<td>78.09</td>
<td>12.62</td>
</tr>
</tbody>
</table>

#### 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.

#### Figure 5. Best Tumor Response

**References**

6. Gerardo Umanzor 1, Rosa Haydee Vassallo 2, Marco Antonio Chivalan Castro 3, Suyapa A. Bejarano 4, Julio Roberto Ramirez Velasquez 5, Ruben Kowalyszyn 6, Luis Enrique Fein 7, John Goldfinch 7, Taryn Moore 7, 1DEMEDICA, San Pedro Sula, Honduras; 2Clinical Research, Dominican Republic; 3CELAN Clínica Médica, Guatemala, Guatemala; 4Centro de Oncología y Medicina Integral del Valle, San Pedro Sula, Honduras; 5Clinica Dr. Julio Roberto Ramirez, Quetzaltenango, Guatemala; 6Instituto de Oncología de Rosario, Rosario, Argentina; 7Athenex, Inc., Buffalo, NY, USA; 8Instituto de Cancerologia, Guatemala, Guatemala.

#### PHASE 3 STUDY DESIGN

- **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 to 21 oral paclitaxel and encequidar: 1 IV paclitaxel across 44 sites in Central and South America (Argentina = 15, Guatemala = 7, Chile = 6).

- **Study Design**
  - Adult female with histologically or cytologically confirmed metastatic breast cancer for whom treatment with IV paclitaxel monotherapy has been recommended by their oncologist
  - 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
  - CNS metastasis
  - Adequate renal function (serum creatinine level <1.5 ULN) and hepatic function (total bilirubin <1.5 ULN)

- **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 48 or 21 cycles (2 or 3 cycles for 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

- **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
  - 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
  - CNS metastasis
  - Adequate renal function (serum creatinine level <1.5 ULN) and hepatic function (total bilirubin <1.5 ULN)
  - 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

- **Adequate hematological status not requiring G-CSF**
- **Adequate renal function (serum creatinine level <1.5 ULN) and hepatic function (total bilirubin <1.5 ULN)**

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

- **Phase 3 Study Summary**
  - At the time of the second DSBM the study was not stopped for futility based on the endpoint of confirmed tumor response. The study is continuing to final analysis
  - Enrollment to the study has been completed
  - Top-line results for confirmed response rate are expected to be available in 2019.

- **References**
  - Dai et al, 2019 Poster #1084 ASCO Chicago, USA