**Background**

- Paclitaxel has poor oral bioavailability due to excretion by intestinal p-glycoprotein.
- Enecouapril (E) is a potent, specific, minimally absorbed p-glycoprotein inhibitor which enables absorption of oral paclitaxel (oPac).
- oPac+E is a combination of Cremophor-free paclitaxel liquid-filled capsules and an enecouapid tablet.
- Systemic exposure (AUC) of oPac-E 205mg/m²/day x 3 is equivalent to IV paclitaxel (IVPac) 80mg/m².
- Concorloster and antiasthma premedications were not required.

**Study Design**

- 402 mBC subjects from Latin America and Dominican Republic were randomized 2:1 to receive oPac 205mg/m²/day x 3 or IVPac 175mg/m² every three weeks; n=137.
- Treatment continued until progression of disease or toxicity. The primary efficacy endpoint was confirmed tumor response rates, greater PFS and greater OS on oPac-E than IVPac (Figure 1; Table 2; Table 3).
- Ongoing studies only enroll patients with hepatic dysfunction.

**Rationale and Methods**

- Subjects with elevated pretreatment liver enzymes or bilirubin were at increased risk of serious early neutropenic complications including sepsis or febrile neutropenia which could be fatal.
- 122 subjects (oPac-E 74; IVPac 48) had elevated pre-treatment AST or serum bilirubin (NICI-ODGW hepatic dysfunction criteria).
- Post-hoc analyses of response rate, safety, PFS and OS in subjects with mild hepatic dysfunction are presented.
- Hazard Ratios, 95.5% Confidence Intervals (CI) were calculated for PFS and OS using a Cox proportional hazards model.

**Results in Mild Hepatic Dysfunction**

- The two treatment groups (oPac-E vs oPac+L) with mild hepatic dysfunction were generally comparable for demographics and disease characteristics (Table 1).
- All but one subject of 122 had mild hepatic dysfunction. The other subject had moderate.
- Mild hepatic dysfunction subjects showed higher response rates, greater PFS and greater OS on oPac-E than IVPac (Figure 1; Table 2; Table 3).
- The clinically significant CIs of the Hazard Ratios of PFS and OS were presented on study deaths occurred in 7% (sepsis or febrile neutropenia n=5) of mild hepatic dysfunction subjects receiving oPac-E vs 0 subjects receiving IVPac.

**Safety in Mild Hepatic Dysfunction**

- Subjects with mild hepatic dysfunction at baseline receiving oPac-E had higher incidence of gastro-intestinal events (nausea, vomiting, diarrhea, abdominal discomfort, and anorexia), fatigue, neutropenia, sepsis, febrile neutropenia, and lower incidence of alopecia, neuropathy, asthenia, arthritis, and myalgia (Table 2).
- On study deaths occurred in 15% of oPac-E and 23% in IVPac in mild hepatic dysfunction subjects.
- Treatment-related deaths occurred in 7% (sepsis or febrile neutropenia n=5) of mild hepatic dysfunction subjects receiving oPac-E vs 0 subjects receiving IVPac.

**Conclusions**

- In the overall trial population, oPac-E was superior to IVPac for the primary endpoint, overall response, as well as for PFS.
- In the subgroup of subjects with mild hepatic dysfunction at baseline, risk of early serious neutropenia as well as infections complications, including treatment-related deaths, was increased.
- This risk is counterbalanced by a potential increase in efficacy in this subgroup.
- Ongoing studies only enroll subjects with intact hepatic function to capitalize on the efficacy of oPac-E while reducing risk of toxicities. (NCT 02545371)