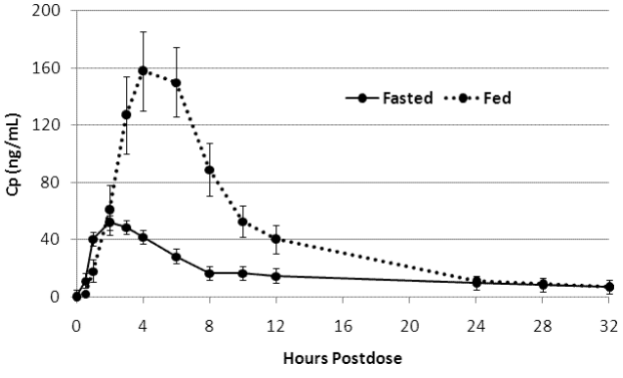
compartment, ANG1005 uses the same receptor-mediated mechanism described above to enter tumor cells where cleavage of ANG1005 occurs, releasing paclitaxel to perform its antimitotic functions. A Phase I clinical trial was initiated in October 2007 to explore the maximum tolerated dose and obtain data on safety, tolerability and preliminary evidence of efficacy of ANG1005 in patients with recurrent malignant glioma.
Material and Methods: A multicenter, open-label, dose escalation study of ANG1005 is being conducted in the United States with sequential dose cohorts ranging from 30–558 mg/m^2. ANG1005 is administered IV over 1 hour every 21 days. Study participants include adult patients with measureable disease and an ECOG performance status $\leqslant$ 2 who are ineligible for standard treatment options.
Results: As of May 26, 7 patients with recurrent malignant glioma have received ANG1005 (4 patients with glioblastoma multiforme, 1 with anaplastic astrocytoma, and 2 with anaplastic oligodendrocytoma). No patient has discontinued from the study due to study drug-related adverse events. The presently enrolling dose is 50 mg/m^2 and escalation is ongoing.
Conclusion: To date, treatment options for patients with recurrent malignant glioma are limited and prognosis is bleak because of the brain's highly evolved physiological structure. Angiopep conjugates may provide a potentially safe and effective way to treat this and other currently unmanageable CNS diseases. ANG1005 is the first of a list of compounds to be tested in this regard.

426 POSTER

Effects of food on the single-dose pharmacokinetics of oral MP-470 capsules

J. Kissling[1], G.D. Fine[2], G.S. Choy[2], C. Eddy[1], G.I. Berk[2]. *[1]MDS Pharma Services, Phase-1 Unit, Lincoln, USA; [2]SuperGen Inc., Clinical Research, Dublin, USA*

Background: MP-470 (MP) is a multi-targeted tyrosine kinase inhibitor which hits a number of validated tumor targets. MP also sensitizes cancer cells to DNA damaging agents and to radiation therapy, presumably through the suppression of Rad51, a key component to the cellular repair machinery in response to DNA double-strand breaks. The HCl salt of MP (MP-HCl) is orally bioavailable and under clinical investigation as single-agent therapy and in combination with standard anticancer agents. Data presented here describe the effect of food on the pharmacokinetics of MP.
Material and Methods: Sixteen healthy volunteer subjects were enrolled into a randomized, 2-period crossover study at MDS Pharma Services (Lincoln, Nebraska, USA). Each subject was to receive a single 700-mg dose of MP on D1 in each of two study periods separated by 7 days rest. Doses were given as seven 100-mg capsules each containing 108.1 mg of MP-HCl. Procedures common to both study periods included admission to the study center the evening before dosing, fasting overnight, swallowing the MP dose with 240 mL water in the morning, and refraining from eating food until 4 hours after dosing. A high-fat, high-calorie breakfast preceded dosing in one of the two study periods. Study period sequence (fed-fasted or fasted-fed) was determined by a randomization schedule stratified by gender. PK blood samples collected predose and at 12 time points up to 32 hours postdose were assayed for MP by Ricerca Biosciences (Concord, Ohio, USA).



Average (±SE) MP-470 plasma concentrations.

Results: Demographic characteristics are 8M/8F; median age 27 years (range 20−43); and median body mass 27.3 kg/m^2 (range 19.9–31.6). All 16 subjects received MP in Period 1, and 15/16 (94%) in Period 2 (1 subject withdrew for personal reasons, and a second subject did not complete scheduled PK blood draws). The only Gr-2 or greater adverse event was Gr-2 headache reported by 2 subjects (13%). There was a pronounced effect of food on the PK of MP with higher exposure following the high-fat, high-calorie breakfast compared to the fasted state (average C_{max} was 196 versus 61 ng/mL [CV 58% and 56%] and average $AUC_{0-\infty}$ was 1541 versus 740 ng·hr/mL [CV 61% and 62%] in the fed and fasted states, respectively). T_{max} was later with food (average 4.8 versus 2.6 hr).
Conclusions: Systemic exposure to MP assessed by C_{max} and $AUC_{0-\infty}$ is increased 3-fold and 2-fold, respectively, following food consumption compared to fasting. Variability of these PK parameters does not appear to be affected.

427 POSTER

Pharmacokinetics (PK) of EZN-2208, a novel anticancer agent, in patients (pts) with advanced malignancies: a phase I dose-escalation study

A. Patnaik[1], M. Goldston[1], C. Takimoto[1], A. Tolcher[1], K. Papadopoulos[1], T. Bekaii-Saab[2], B. Kleiber[2], F. Gamza[3], C. Longley[4], A. Buchbinder[3]. *[1]START (South Texas Accelerated Research Therapeutics), Clinical Research, San Antonio, TX, USA; [2]Ohio State University, Medicine and Pharmacology, Columbus, USA; [3]Enzon Pharmaceuticals Inc., Clinical Development, Bridgewater, USA; [4]Enzon Pharmaceuticals Inc., Toxicology, Piscataway, USA*

Background: EZN-2208 is a water-soluble, polyethylene glycol (PEG) conjugate of SN38 that is active in a broad spectrum of preclinical models, including an *in vivo* CPT-11-resistant tumor model. EZN-2208 accumulates in tumors, where it releases SN38.
Methods: Pts with advanced solid tumors were enrolled to determine the safety, tolerability, PK, maximum tolerated dose, recommended dose, and preliminary evidence of antitumor activity of EZN-2208 administered as a 1-h IV infusion, weekly x 3 per 4-week cycle, in a 3+3 escalating-dose design. Dose escalation was based on drug-related toxicities during the first cycle. PK samples were obtained after the first and third doses. Plasma concentrations of EZN-2208, SN38, and SN38G were determined by HPLC using fluorescence detection. PK parameters were estimated using a noncompartmental model analysis.
Results: 12 pts (7 females; median age = 61 y [39−85]) were treated at doses of 1 (3 pts), 2 (3 pts), 3.3 (3 pts), and 5 (3 pts) mg/m^2. 11 pts had received multiple prior therapies (median prior regimens = 3; range = 1–8). Tumor types included colorectal cancer (CRC) (5 pts); melanoma (1 pt); and anal, breast, esophageal (E), gastric, ovarian, and pancreatic cancer (1 pt each). Pts have received 1 to 7 treatment cycles. The most common adverse events (AEs) were nausea (6 pts); diarrhea and fatigue (4 pts each); and constipation, vomiting, and anorexia (3 pts each). Most AEs were Grade 1 or 2. No dose-limiting toxicities have been observed to date. Stable disease was observed in 1 pt with E cancer (120 days) and 3 pts with CRC (57, 57, and 216+ days). Plasma PK for the first 3 cohorts (9 pts) is provided in the table.
Conclusions: EZN-2208 was well tolerated. Qualitative assessment shows the AUCs of EZN-2208 increased proportionally with increasing dose. The SN38 t1/2 was independent of dose. There was no accumulation of EZN-2208 or SN38 after weekly dosing for 3 of 4 weeks. Dose escalation is ongoing; updated clinical and PK data will be presented.

PK Parameters After First Dose of First Cycle

	EZN-2208[b]			SN38[b]		
Dose[a] (mg/m^2)	Cmax[a] (μg/mL)	AUC(0-inf)[a] (h·μg/mL)	Terminal t/12 (h)	Cmax (ng/mL)	AUC(0-t)[c] (h·ng/mL)	Terminal t/12 (h)
1	14.9±1.8	459.8±37.5	53.3±30.5	57.3±13.3	1388±293	26.5±4.6
2	29.8±6.4	919.9±174.9	32.9±6.7	11.7±7.7	228±77	24.2±2.9
3.3	40.1±24.5	1140.3±739.5	21.3±4.9	11.5±7.0	227±179	27.3±3.3

[a]SN38 equivalents; [b]Mean±standard deviation; [c]AUC(0−t), t is time of last measurable concentration.

428 POSTER

A phase I dose-escalation study of TAS-102, a novel oral functional antitumor nucleoside, administered twice daily to Japanese patients (pts) with advanced solid tumors

Y. Onozawa[1], N. Boku[1], A. Fukutomi[1], A. Ohtsu[2], T. Doi[2], T. Yoshino[2], W. Koizumi[3], S. Tanabe[3], T. Sasaki[3]. *[1]Shizuoka Cancer Center, Division of Gastrointestinal Oncology, Shizuoka, Japan; [2]National Cancer Center Hospital East, Division of GI Oncology – Digestive Endoscopy, Kashiwa, Japan; [3]Kitasato University East Hospital, Department of Gastroenterology, Kanagawa, Japan*

Background: TAS-102 consists of trifluorothymidine (FTD) and an inhibitor of thymidine phosphorylase (TPI). FTD is an inhibitor of thymidylate