**Pharmacokinetics of a Trypsin-Labile Extended-Release Hydromorphone Prodrugs in Healthy Volunteers**

Steven Shafer, MD, Stanford University, Craig Husfeld, PhD, Signature Therapeutics, Judy Magruder, MBA, Signature Therapeutics

**Background/Introduction:** We have created a trypsin-labile extended-release prodrug of hydromorphone. The first study in man addressed four questions: 1) is the drug safe, 2) does the prodrug convert to hydromorphone and is that conversion dose-proportional, 3) does the prodrug increase the variability in hydromorphone concentrations, and 4) does food affect the bioavailability of hydromorphone following oral ingestion of hydromorphone prodrug?

**Methods:** Following institutional approval and written informed consent, we recruited 51 subjects for a randomized, blinded dose escalation study comparing the pharmacokinetics of an orally administered hydromorphone solution (12 subjects, 0.5 to 24 mg hydromorphone) with an orally administered solution of hydromorphone prodrug (39 subjects, 1 to 48 mg hydromorphone prodrug). In the dose escalation study, all subjects received naltrexone to block opioid drug effects. In the food effect study, following institutional approval and written informed consent 12 additional subjects received 16 mg of oral hydromorphone prodrug solution in each of two sessions. Subjects were randomly assigned to no breakfast or a standard high fat breakfast 30 minutes before drug administration. Pharmacokinetics were determined by venous blood samples drawn at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, 60, and 72 hours after drug administration. The food effect subjects did not receive naltrexone to allow for opioid drug effect on gastrointestinal motility.

**Results:** Plasma hydromorphone levels following oral administration of hydromorphone in solution peaked in less than one hour of administration. Plasma hydromorphone levels following oral administration of hydromorphone prodrug in solution peaked 3-4 hours after drug administration. Estimation of the relative bioavailability of hydromorphone from the prodrug vs from hydromorphone suggests a ratio of oral hydromorphone prodrug to oral hydromorphone of 2.8:1. Plasma hydromorphone concentration increased linearly with dose in both groups. The inter-subject variability in plasma concentration following administration of oral hydromorphone in solution was greater than the intersubject variability of hydromorphone following administration of hydromorphone prodrug. Food did not significantly affect the pharmacokinetics of the oral hydromorphone prodrug. There were no serious adverse events.

**Conclusions:** The pharmacokinetics of the trypsin-labile extended-release hydromorphone prodrug in man were accurately predicted by prior animal studies. The molecular mechanism of hydromorphone release produced a peak concentration of hydromorphone 3-4 hours after drug administration. Since the construction of the prodrug and therefore opioid delivery, is a function of covalent chemistry, it cannot be defeated by physical manipulation (e.g., chewing). The pharmacokinetics are linear with respect to dose, have lower intersubject variability than oral hydromorphone solution, and do not demonstrate a significant food effect. These findings support further clinical development of our trypsin-labile extended-release hydromorphone prodrug.

**Acknowledgment:** The contributions of Dennis Fisher (P Less Than); Alex Konstantatos (Department of Anesthesia and Perioperative Pain Management, Alfred Hospital, Monash University, Melbourne, VIC 3004, Australia); Peter Hodsman (Nucleus Network Limited, Melbourne, VIC 3004, Australia) and Thomas Jenkins, PhD, to this work are gratefully acknowledged.