**Opioid Prodrug for Immediate-Release Hydrocodone**

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

**Purpose:** Every year in the United States prescription opioid abuse is responsible for tens of thousands of deaths and tens of billions of dollars in increased health care costs. Our goal was to create a trypsin-labile opioid prodrug of hydrocodone that provided an immediate-release profile following oral ingestion but was inactive following parenteral (IV) administration.

**Methods:** Signature Therapeutics’s prodrug of hydrocodone was designed to release hydrocodone via a two-step process including: 1) bioactivation by trypsin, followed by 2) a rapid cyclization-release reaction. Key molecular components include a chemically robust, N-substituted carbamate functionality that covalently attaches the hydrocodone to a cyclic diamine linker, which is terminally substituted with a N-acylated L-arginine (amino acid). Upon oral dosing and exposure to trypsin, the amino acid component is cleaved by enzymatic hydrolysis, exposing a conformationally-restrained nucleophilic terminal amine. The otherwise stable carbamate linkage undergoes intramolecular attack from the exposed nucleophilic terminal amine, resulting in liberation of hydrocodone at a controlled rate. Steric manipulation of the diamine linker has been optimized for rapid cyclization, resulting in immediate-release of hydrocodone following trypsin digest. We measured the *in vitro* rate of appearance of opioid following exposure to trypsin, as well as the time course of systemic opioid in rats and dogs following oral and intravenous administration. We also measured the ability of the hydrocodone prodrug to cross into the central nervous system (rat) and the activity at the μ-opioid receptor.

**Results:** Following *in vitro* exposure to trypsin, cleavage of the amino acid component of the hydrocodone prodrug was rapid (t1/2 < 5min). The *in vitro* half-life for the subsequent intramolecular attack, forming cyclic urea and releasing the opioid moiety, was less than 5 minutes under physiological conditions. Following oral administration of the hydrocodone prodrug to dogs, the hydrocodone concentration peaked ~30 minutes after oral administration. Following intravenous administration of the hydrocodone prodrug to rats and dogs, less than 0.1% of the prodrug was converted to the parent opioid. The hydrocodone prodrug had 7% the potency of hydrocodone at the μ-opioid receptor, and 1.1% the penetration across the blood brain barrier (rat), resulting in < 0.1% of the opioid activity of intravenous hydrocodone.

**Conclusions:** We have created a trypsin-labile, immediate-release prodrug of hydrocodone that releases the parent opioid following oral administration. Minimal conversion of the hydrocodone prodrug to hydrocodone occurs following parenteral (IV) administration. The hydrocodone prodrug has minimal ability to reach and activate the μ-opioid receptor within the central nervous system.

**Acknowledgment:** The contribution of Thomas Jenkins, PhD, to this work is gratefully acknowledged