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First-In-Human Pharmacokinetics and Safety Study of Pf614: Orally Activated Oxycodone Prodrug

William K. Schmidt[1], Daniel S. Dickerson[2], Dennis M. Fisher[3], D. L. Kirkpatrick[1]
[1]Ensysce Biosciences, San Diego, CA, [2]PRA Health Sciences, Lenexa, KS, [3]P Less Than, San Francisco, CA

Introduction: PF614 is an extended-release abuse deterrent prodrug of oxycodone for oral use in chronic pain. PF614 is designed to limit use to oral administration since it remains pharmacologically inactive via i.v. or nasal administration.[1] Upon ingestion, a 2-step activation process releases oxycodone through (1) trypsin bioactivation to provide intermediate PFR06082 and (2) a subsequent intramolecular cyclization-release of cyclic urea (PFR06110) and oxycodone. PF614 cannot be activated via intravenous (i.v.), nasal, or other routes of administration that do not provide exposure to pancreatic trypsin. Additionally, Laboratory Manipulation and Extraction Studies (FDA Category 1) demonstrate that PF614 cannot be hydrolyzed or extracted to produce oxycodone using common household chemicals, solvents, or OTC enzyme preparations. A Phase 1 clinical study to assess PF614 for safety and pharmacokinetic properties, to verify oxycodone release in an extended release profile is underway.

Methods: Clinical study PF614-101, initiated November 2016, is a Single Ascending Dose (SAD) open-label comparison in healthy subjects randomized to receive an oral liquid solution formulation of PF614-101 (15 mg and higher; n=6 subjects per cohort) or oxycodone HCl ER tablets (OxyContin®, 10 mg and higher; n=2 subjects per cohort). The study will enroll up to 8 cohorts of men and women (18-50 years old). Cohort 1 was tested in a cross-over fashion with and without naltrexone blockade; all subsequent cohorts receive concomitant naltrexone to prevent opioid respiratory depression. The pharmacokinetic evaluation is designed to provide C_{max}, T_{max}, AUC and $t_{1/2}$ for the oxycodone release from both PF614 and oxycodone HCl ER tablets, the parent PF614, and metabolites, PFR06082 and PFR06110. Study details are available at ClinicalTrials.gov, ID # NCT02454712.

Results: Pharmacokinetic and safety data from the first 2 cohorts demonstrate that PF614 is activated to release oxycodone with high efficiency. Oxycodone release from PF614 (15 and 25 mg) yields a median $T_{max}$of 5.0 hr (range 3-8 hr; n=16) and median $t_{1/2}$ of 9.7 hr (range 5-16 hr). PF614, 25 mg, appears bioequivalent to 10 mg of oxycodone HCl ER tablets. Systemic exposure to the prodrug was minimal in all subjects, confirming that it is converted to active oxycodone in the GI tract and oxycodone is then absorbed as efficiently as from oxycodone HCl ER tablets. Adverse events were consistent with naltrexone and opioid use including nausea, emesis and somnolence in a limited number of subjects.

Conclusion: PF614 represents a new approach to developing abuse-deterrent opioids by limiting oxycodone release to oral administration. The pharmacokinetic data to date demonstrates an extended release profile for oxycodone that supports a twice-a-day dosing regimen. Safety data also suggests PF614 is well tolerated with no unexpected safety concerns at the doses evaluated.

Reference(s):
1. J Opioid Manag, in press, 2017

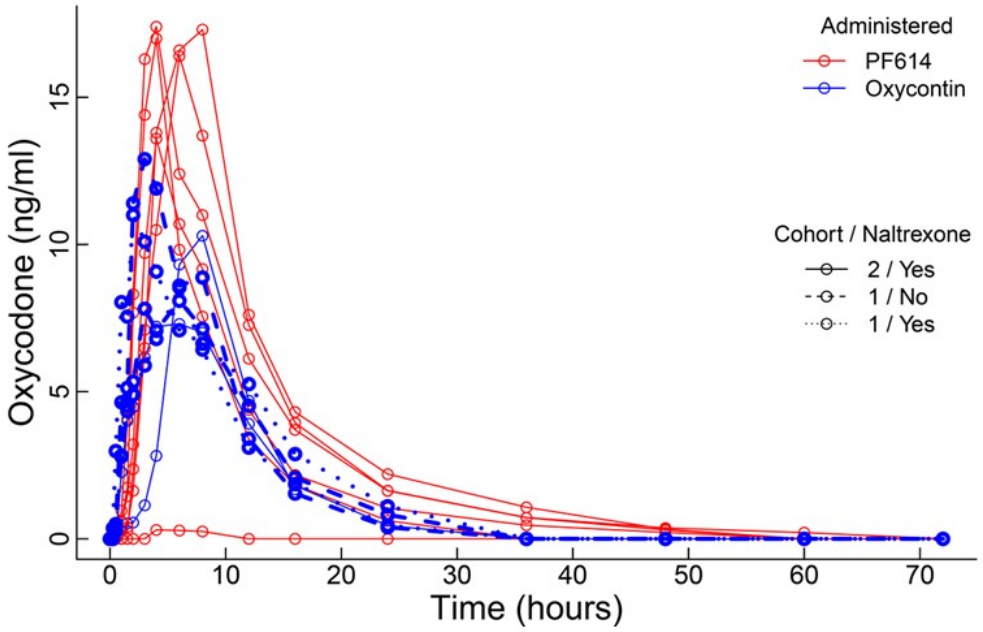

Fig. 1: PF614 (25 mg) vs. OxyContin® (10 mg). PF614 doses (n=5) were tested in the presence of an opioid-blocking dose of naltrexone. OxyContin doses (n=6) were tested both in the presence and absence of naltrexone.