First-in-Human Pharmacokinetics & Safety Study of PF614: Orally Activated Oxycodone Prodrug

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Introduction

PF614 is an abuse deterrent prodrug of oxycodone for use in chronic pain. PF614 is designed to limit use to oral administration since it remains pharmacologically inactive via IV or nasal administration. Upon ingestion, oxycodone is released through two steps:

(1) trypsin bioactivation to intermediate PFR06082 (releasing PFR06116), and
(2) trypsin-induced cyclization-release of oxycodone and cyclic urea (PFR06110).

PF614 is not activated via IV, 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 is not hydrolyzed or extracted to produce oxycodone using common household chemicals, solvents, or OTC enzyme preparations[1].

We conducted a single-ascending dose (SAD) Phase 1 study to assess PF614 for safety and pharmacokinetic (PK) properties and to verify that PF614 yields an extended release profile for oxycodone.

Methods

PF614-101 (conducted 11/2016 – 04/2017) is an open-label study in 6 cohorts of healthy men and women (18-50 years) randomized to receive PF614-101 (liquid formulation; 15-200 mg) or oxycodone HCl ER (OxyContin® tablets, 10-80 mg). Cohort 1 was tested with and without naltrexone blockade (cross-over); subsequent cohorts received naltrexone to prevent respiratory depression. Subjects were fasted except for Cohort 6 which received a high-fat, high calorie meal 30 min prior to dosing. Non-compartmental PK analyses were conducted for oxycodone release from both PF614 and OxyContin, and for the parent PF614 and metabolites PFR06082 and PFR06110. Additional details are available at ClinicalTrials.gov, ID # NCT02454712.

Cohort #	Naltrexone	Fed Status	Dose (mg)	
	Yes/No		PF614	OxyContin
1	8/8	Fasted	15 (n=12) *	10 (n=4) †
2	0/8	Fasted	25 (n=6)	10 (n=2)
3	0/8	Fasted	50 (n=6)	20 (n=2)
4	0/8	Fasted	100 (n=6)	50 (n=2)
5	0/8	Fasted	200 (n=6)	80 (n=2)
6	0/8	High-fat meal	200 (n=8)	—

* N=6 with naltrexone, N=6 without naltrexone

† N=2 with naltrexone, N=2 without naltrexone

Results

- Based on AUC, PF614 releases oxycodone with 90-95% efficiency throughout the dose range tested
- Based on C_{max} and AUC, PF614 yields dose-proportional exposure to oxycodone
- Oxycodone released from PF614 has a median half-life of 13.7 hr vs. 7.4 hr for OxyContin (all cohorts)
- Food and naltrexone affected PF614 PK parameters minimally
- No unexpected adverse effects

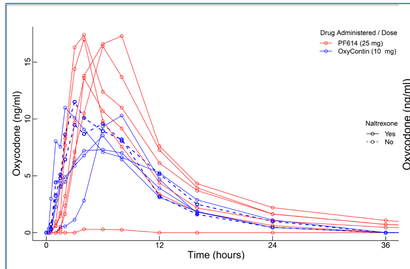

Fig. 1a: **Oxycodone plasma exposure (Cp); PF614 (Cohort 2) and OxyContin® (Cohorts 1 and 2).** Cohort 1 was tested in the presence and absence of naltrexone (crossover). Subsequent cohorts were tested only in the presence of naltrexone. One PF614 subject vomited within 1 min of dosing, so exposure was extremely low as shown.

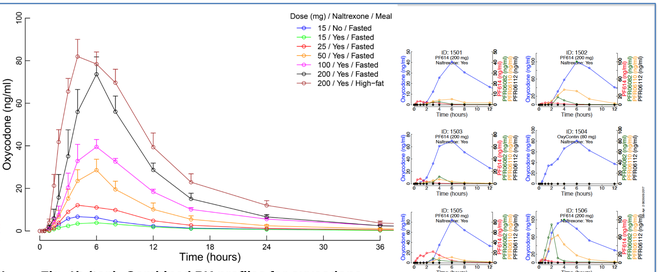

Fig. 1b (top): Combined PK profiles for oxycodone released from 15-200 mg PF614 (approx. 6 to 80 mg OxyContin equivalent). Mean + SE values shown.

Fig. 1c (right): Individual subject profiles for PF614, oxycodone, and prodrug fragments following a single 200 mg dose of PF614 (n=6) or 80 mg OxyContin (n=2).

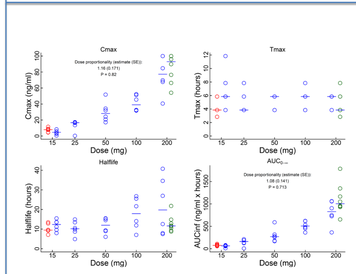

Fig. 2: **Oxycodone PK parameters derived from PF614 (15-200 mg)**. Red = no naltrexone. Blue = with naltrexone. Green = high-fat, high calorie meal. Horizontal line = median.

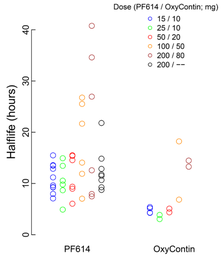

Fig. 3: **Comparison of half-lives of PF614 (15-200 mg) vs. OxyContin (10-80 mg).**

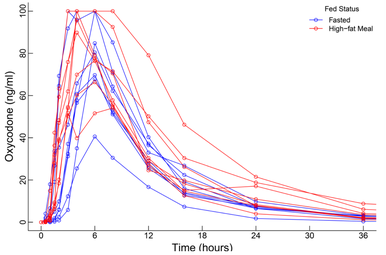

Fig. 4: **PF614 (200 mg) in fed vs. fasted subjects.** Oxycodone T_{max}, C_{max}, and AUC were similar in fed vs. fasted state. Values for all subjects shown.

Conclusions

- PF614's PK profile supports b.i.d. dosing
- "Clock" (Fig. 5) can be fine-tuned chemically to IR or ER release
- PF614 is inactive by itself; requires activation via G.I. trypsin
- PF614 is not activated via IV administration
- PF614 cannot be activated via generic trypsin products or *in vitro* manipulation

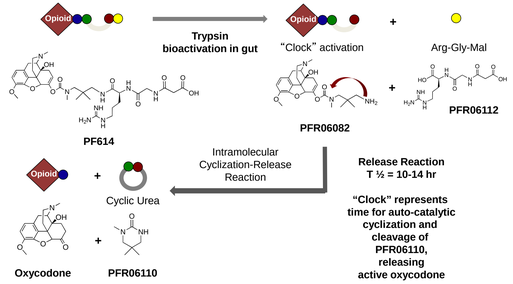

Fig. 5: Mechanism of bioactivation and subsequent cyclization to oxycodone from PF614. PF614 molecular weight = 756.85 g/mol; oxycodone HCl molecular weight = 351.83 g/mol; molar ratio = 2.15x.

Next Steps

- Multiple Ascending Dose (MAD) Study
- Human Abuse Liability (HAL) Studies

Reference

1. Kirkpatrick DL, *et al*. In vitro and in vivo assessment of the abuse potential of PF614, a novel BIO-MD™ prodrug of oxycodone. J Opioid Manag. 2017;13:39-49.