The Next Generation Opioid Products for Moderate-Severe Pain

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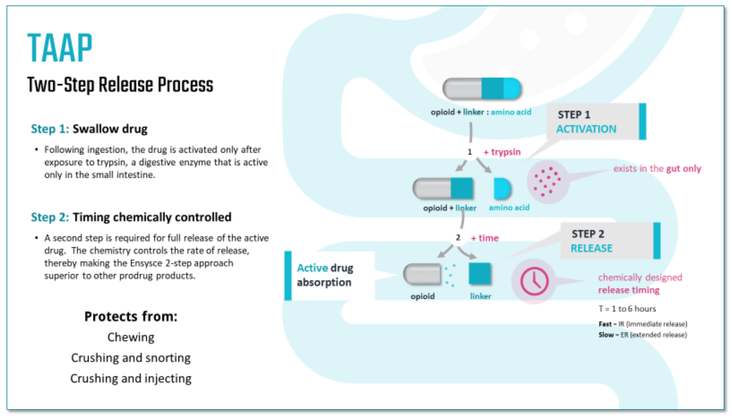
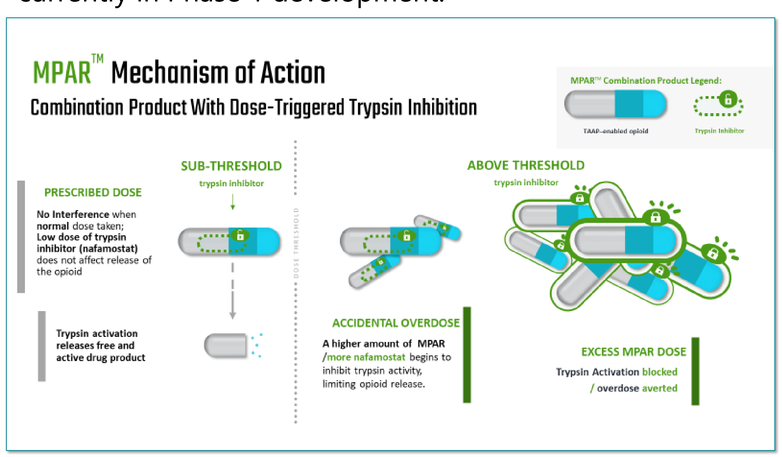
Introduction

Opioid abuse is a major societal burden, resulting in significant costs and overdose deaths. Ensysce is developing the "Next Generation" of opioid prodrug products to overcome fear, stigma and reluctance of physicians to prescribe and patients to take opioids for severe pain. Our technologies are designed to deter prescription opioid abuse by controlling bioavailability through unique prodrug chemistry providing **2-step Trypsin Activation Abuse Protection** [**TAAP**] illustrated below. Our lead TAAP opioid, PF614 has been evaluated in Phase 1 single ascending dose (SAD) and multi-ascending dose (MAD) studies, with novel data provided here for the MAD study.



TAAP prodrugs combined with the trypsin inhibitor, nafamostat, provide overdose protection when more than prescribed doses are consumed. This overdose protection is the Multi-Pill Abuse Resistance, **MPAR,** PF614-MPAR is currently in Phase 1 development.



Methods

PF614-102 MAD study was an open-label study in 6 cohorts of healthy men and women (18-50 years) randomized to receive PF614 n=6 (liquid formulation; 50-100 mg or 2 x 100 mg capsules) or oxycodone HCl ER n=2 (OxyContin® tablets, 20-80 mg). All cohorts received naltrexone to prevent respiratory depression. Subjects were fasted. Non-compartmental PK analyses were conducted for oxycodone release from both PF614 and OxyContin. Additional details are available for the Phase 1 SAD and MAD studies at ClinicalTrials.gov, NCT02454712 and NCT05043766.

Results

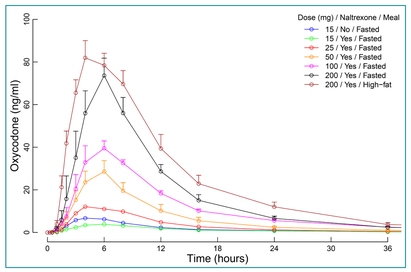


Fig. 1: Combined PK profiles for oxycodone released from 15-200 mg PF614 (approx. 6 to 80 mg OxyContin equivalent). Mean ±SE values shown. Phase 1 SAD study

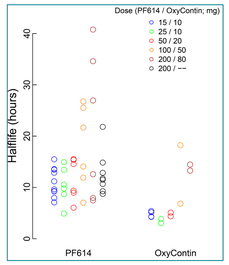


Fig. 2: Comparison of half-lives of PF614 (15-200 mg) vs. OxyContin (10-80 mg). Phase 1 SAD study

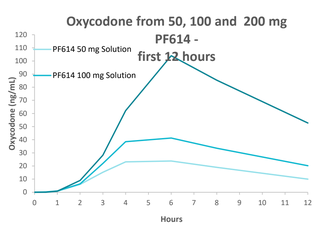


Fig. 3: Oxycodone PK parameters derived from PF614 (50 - 200 mg) delivered as oral solution or as 100 mg capsules. Phase 1 MAD study

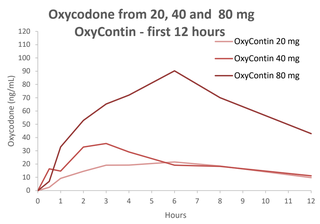


Fig. 4: Oxycodone PK parameters derived from OxyContin (20 - 80 mg) delivered orally. Phase 1 MAD study

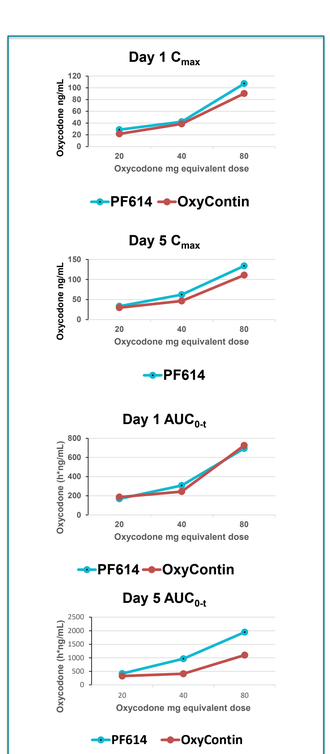


Fig. 5: Oxycodone C_{max} and AUC days 1 and 5 derived from PF614 (50 to 200 mg) or OxyContin (20 - 80 mg) delivered orally. Phase 1 MAD study

Results

Table of Adverse Events

	PF614 50 mg n=6 n (%)	OxyContin 20 mg n=2 n (%)	PF614 100 mg n=6 n (%)	OxyContin 40 mg n=2 n (%)	PF614 200 mg n=6 n (%)	OxyContin 80 mg n=2 n (%)
Total subjects with at least 1 TEAE*	2 (33.3)	1 (50.0)	1 (16.7)	1 (50.0)	6 (100.0)	2 (100.0)

- **SAD Phase 1a:** Based on AUC for, PF614 releases oxycodone with ~90% efficiency and yields dose-proportional exposure to oxycodone. Oxycodone released from PF614 has a median half-life of 12.7 hr vs. 7.4 hr for OxyContin (all cohorts) SAD study.
- **MAD Phase 1b:** Based on C_{max} and AUC, PF614 dose-proportional exposure to oxycodone comparable to that released from OxyContin at a 2.5:1 ratio.
- BID dosing of PF614 or OxyContin provides oxycodone with similar C_{max} values over a 5 day period. Both PF614 and OxyContin show some accumulation with larger AUCs after 5 days of BID dosing.
- No unexpected adverse effects were observed in either the SAD or MAD study.

Conclusions

- The TAAP opioid, PF614 b.i.d. dosing will provide around the clock pain relief.
- **PF614 is inactive by itself; requires activation via G.I. trypsin following oral ingestion. PF614 is not activated following IV administration.**
- PF614-MPAR, a combination product with trypsin inhibitor in Phase 1 development, is designed to provide overdose protection.

Next Steps

Nasal and Oral Human Abuse Liability (HAL) Studies (in progress).

Reference

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.