PF614-MPAR: A Novel Trypsin Activated Abuse Protected (TAAP™) Extended-Release Oxycodone Prodrug with Overdose Protection

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FDA Breakthrough Designation

Introduction

Opioid abuse, a major societal burden, results in significant costs and overdose deaths. Ensysce's "Next Generation" opioids use a chemical approach to reduce abuse (**TAAP™**) and overdose (**MPAR®**). These 2 new approaches should allow the relief of severe pain with lower abuse, less anxiety, ease of use, and fewer overdoses.

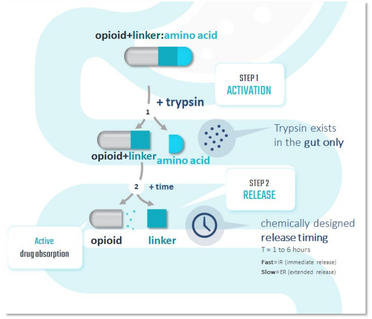
Ensysce's Two Core Technology Platforms Driven by Chemistry

TAAP™: Reducing abuse

Trypsin Activated Abuse Protection

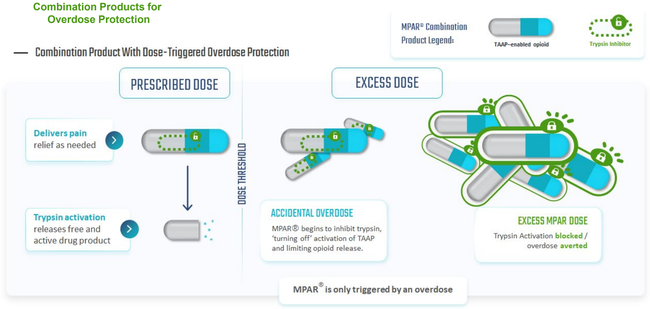
Two Step Activation

1. **Swallow**: trypsin 'turns on' activation
2. **Chemically controlled release** for immediate and extended-release products.



MPAR®: SMART overdose protection

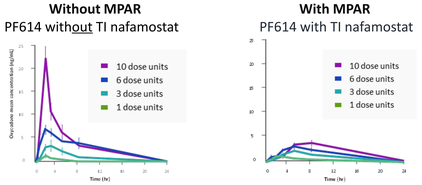
Multi-Pill Abuse Resistance: Combination Products for Overdose Protection



Methods

PF614-MPAR

Combination Product: TAAP-PF614 oxycodone prodrug with and without trypsin inhibitor (TI), nafamostat.

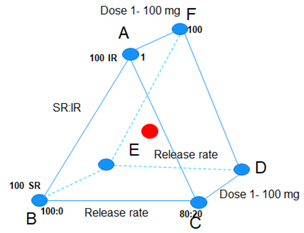


Goal of project:

1. To identify formulation of nafamostat for the PF614-MPAR drug product to produce overdose protection in humans as was illustrated in animal studies (above).
2. To evaluate formulated nafamostat combinations with PF614 in a Phase 1 clinical trial with healthy volunteers.

Ensysce used the Quotient Sciences Translational Pharmaceutics platform to manufacture formulated nafamostat, to define a 'design space' of "dose" and "release rate" to test clinically and to undertake the Phase 1 clinical study.

Prism design space – 3 dimensional



Hypothetical design space to allow clinical testing of **3** variables including release rate of extended-release (ER) nafamostat beads, ratio of immediate release (IR) to ER and total dose of nafamostat. Red dot represents mid point of each variable.

Results

Optimization of PF614-MPAR composition

- **PF614** was used at a constant 25 mg dose through-out the study, to deliver 10 mg oxycodone (**Figure 2A**).
- **Nafamostat** total dose in a simulated overdose situation was chosen to be ≤10 mg.
- Variables tested:
  - ER bead release rate
  - ER:IR ratio
  - Nafamostat dose

The Quotient platform allowed the alteration of nafamostat formulation through progression of each cohort, to ultimately identify the optimal combination of dose and release rate for nafamostat.

GOALS:

- **PF614** to release **oxycodone** at a prescribed dose (1 or 2 dose units).
- **Nafamostat** to **block oxycodone release** if **overdose** is taken.

Ultimately, the optimal PF614-MPAR 25 mg dose unit was defined.

Comparing PF614 delivered alone or with 10 mg IR nafamostat

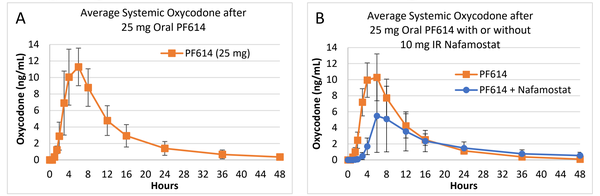


Figure 2: Simulated overdose protection: Oxycodone release from PF614 when delivered alone **(A)** or in combination with 10 mg nafamostat IR solution (**B**).

Comparing nafamostat bead release and IR:ER ratio

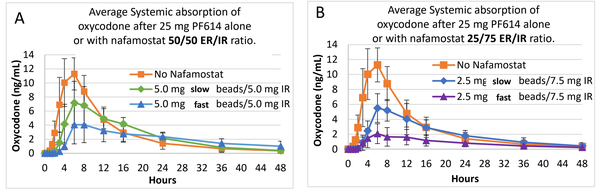


Figure 3: Inhibition of PF614 oxycodone release using different bead release rates and nafamostat composition: A: 10 mg nafamostat composition of either slow or fast releasing ER beads (5 mg) and IR solution (5 mg); **B:** 10 mg nafamostat composition of either slow or fast releasing ER beads (2.5 mg) and IR solution (7.5 mg);

Results

Overall improvement of overdose protection through Phase 1 study

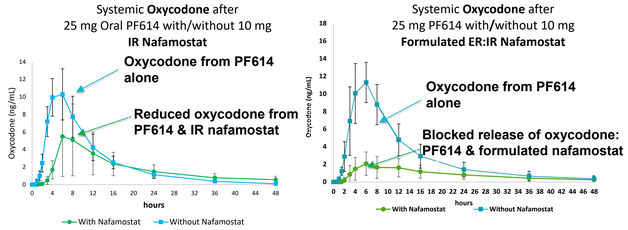


Figure 4: Phase 1A: Simulated overdose protection: A: IR nafamostat 10 mg or B: Optimal nafamostat formulation (10 mg) with 25 mg PF614 administered.

PF614-MPAR Pain Relief with Overdose Protection

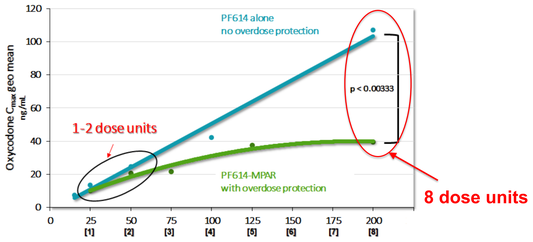


Figure 5: Phase 1B: PF614-MPAR 25 mg (PF614 25 mg with 1 mg nafamostat) administered simultaneously at 1 to 8 dose units.

Conclusions

- The Phase 1 study defined the final nafamostat formulation comprised of the optimal release rate and optimal ratio of IR and ER nafamostat for the PF614-MPAR 25 mg dose (PF614 25 mg + formulated nafamostat 1 mg).
- The **PF614-MPAR 25 mg** formulation delivers oxycodone as designed when 1 or 2 doses were delivered simultaneously to healthy subjects, but *reduced oxycodone release at 3 or more simultaneous dose units.*
- PF614 and nafamostat combinations tested were **safe and well tolerated**.
- **PF614-MPAR could be the first opioid product with *abuse resistance* and *overdose protection*.**