Preventing Prescription Drug **Overdoses:** Clinical development of **Trypsin-Activated Abuse Deterrent** (TAAP) Opioids with Overdose Protection

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Disclosures

 Dr. Schmidt is the Chief Medical Officer and a senior executive of Ensysce Biosciences, a publicly-traded La Jolla, CA-based pharmaceutical company that is developing Trypsin-Activated Abuse Deterrent (TAAP) opioids. Phase 3 clinical trials will be initiated in H2 2024.



Learning Objectives

- Objective 1: Introduce an entirely new class of opioid-class analgesics that will be significantly safer and less abusable than ADF formulations
- Objective 2: Show how overdose protection can be achieved by limiting opioid exposure if an individual takes 3-8 capsules or tablets simultaneously
- **3. Objective 3**: Highlight Phase 1 & 2 clinical data showcasing how PF614 combined with nafamostat achieves Objectives 1 & 2.



The Problem: Rx Opioid Overdoses

National Overdose Deaths Involving Prescription Opioids, Number Among All Ages, 1999-2021



Source: https://nida.nih.gov/research-topics/trends-statistics/overdose-death-rates

- There are more than **45 deaths** each day in the U.S. from **prescription opioids overdose** (16,706 deaths in 2021).
- Currently marketed 'abusedeterrent-formulation' (ADF) opioids fall short of providing a solution to curb opioid abuse, and none are designed to prevent oral overdose.
- Illicit opioids (e.g. street fentanyl) increase the total 2021 opioid deaths to

106,200 individuals.



Step 1: PF614 = TAAP Oxycodone Prodrug

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.



- **PF614** is a chemically modified
 Trypsin-Activated Abuse
 Protected (TAAP) oxycodone
 prodrug that is activated to
 release oxycodone only when
 exposed to the enzyme trypsin in
 the small intestine.
- Trypsin is not in other tissues in the body.



Step 2: PF614 + Nafamostat = Multi-Pill Abuse Resistance (MPAR)

MPAR[®]: SMART overdose protection



- **PF614-MPAR** is a TAAPoxycodone combined with nafamostat to provide overdose protection
- Nafamostat is a potent trypsin inhibitor.
- The intent is to provide analgesia at a prescribed dose, yet if more than a prescribed dose is consumed simultaneously, the increased amount of trypsin inhibitor will block further activation reducing release of the active opioid, averting an overdose.



Step 3: Proof of Principle, PF614 + Nafamostat

PF614-MPAR Pain Relief with Overdose Protection



PF614 (mg) or PF614-MPAR [# dose units]

- 1-2 doses of PF614-MPAR delivered oxycodone at the same level as PF614 alone.
- At 3 doses, oxycodone was reduced compared to 3 doses of PF614 alone.
- At 8 doses, there was a significant decrease (p<0.00333) in the maximal oxycodone plasma concentration (Cmax) compared to PF614 alone.



Summary & Conclusions

- In a Phase 1 clinical trial, we were able to optimize the PF614-MPAR drug combination and undertake a proof-of-concept trial to successfully test its overdose protection.
- PF614 alone will enter Phase 3 clinical studies in H2 2024.
- PF614-MPAR combination will enter a Phase 1b study to optimize dosage strengths, then a multi ascending dose (MAD) study to evaluate PK and safety.
- Stay tuned! The TAAP and MPAR technology can be applied to many types of drugs to reduce abuse and overdose potential

Bonus: The FDA designated PF614-MPAR as a "Breakthrough Therapy" in January 2024.



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