

# IMPROVING PRESCRIPTION DRUG SAFETY THROUGH CHEMISTRY

**NASDAQ: ENSC** 



#### **Disclaimer**

Ensysce's PF614 and nafamostat are currently in clinical trial and pre-clinical studies, involving both the TAAP platform and MPAR platform. Accordingly, PF614 and nafamostat have the risks and uncertainties inherent in any drug in trial-phase, which include, but are not limited to, a failure to show sufficient efficacy to obtain FDA approval, the risk that clinical trials may not confirm any safety, potency or other product characteristics described or assumed herein and the possibility that presently unknown safety risks may occur. The statements made concerning PF614, nafamostat, TAAP and MPAR are subject to the complete set of risks set forth in the Risk Factors disclosure found in the Company's most recent Annual Report on Form 10-K filed with the Securities and Exchange Commission on March 30, 2023.

### **Forward Looking Statements**

Statements contained in this presentation that are not purely historical may be deemed to be forward-looking statements for the purposes of the safe harbor provisions under The Private Securities Litigation Reform Act of 1995 and other federal securities laws. Without limiting the foregoing, the use of words such as "may," "intends," "can," "might," "will," "expect," "plan," "believe" and other similar expressions are intended to identify forward-looking statements. The product candidates discussed are in clinic and not approved and there can be no assurance that the clinical programs will be successful in demonstrating safety and/or efficacy, that Ensysce will not encounter problems or delays in clinical development, or that any product candidate will ever receive regulatory approval or be successfully commercialized. All forward-looking statements are based on estimates and assumptions by Ensysce's management that, although Ensysce believes to be reasonable, are inherently uncertain. All forward-looking statements are subject to risks and uncertainties that may cause actual results to differ materially from those that Ensysce expected. In addition, Ensysce's business is subject to additional risks and uncertainties, including among others, the initiation and conduct of preclinical studies and clinical trials; the timing and availability of data from preclinical studies and clinical trials; expectations for regulatory submissions and approvals; potential safety concerns related to, or efficacy of, Ensysce's product candidates; the availability or commercial potential of product candidates; the ability of Ensysce to fund its continued operations, including its planned clinical trials; the dilutive effect of stock issuances from fundraising; and Ensysce's and its partners' ability to perform under their license, collaboration and manufacturing arrangements. These statements are also subject to a number of material risks and uncertainties that are described in Ensysce's most recent Annual Report on Form 10-K. Any forward-looking statement speaks only as of the date on which it was made. Ensysce undertakes no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events or otherwise, except as required under applicable law





## OVERVIEW: Platform Technology – Abuse and Overdose Protection

— Two Clinical Programs in Development





Trypsin-Activated
Abuse Protection

### **MPAR®**

Multi-Pill Abuse Resistance: Combination Product for Overdose Protection

...to deliver improved drug performance.



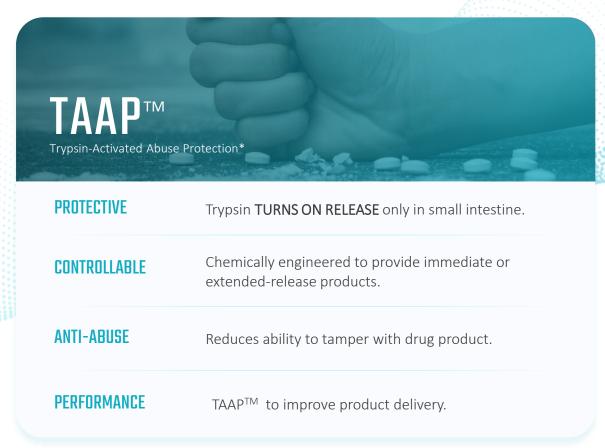
### Immediate focus – severe pain

- > Delivering 'Next Generation' opioid products
- > Strong efficacy with less abuse and overdose potential



### TAAP<sup>TM</sup> and MPAR<sup>®</sup>

— Improving Drug Performance and Safety Through Chemistry





SMART	TURNS OFF RELEASE only with overdose.
COMBINATION	Trypsin inhibitor, nafamostat added to TAAP products.
UNIQUE	Platform based on trypsin control of activation and release.
MULTI-USE	$TAAP^{TM}$ and $MPAR^{\$}$ can be applied to numerous drug classes.

<sup>\*</sup>For mechanism see appendix



**Dueling Crises: Pain vs Abuse and Overdose** 

— Pain is the Leading Cause of Doctor Visits



35 Million

Americans in severe pain



10 Million

Misuse Opioids



143 Million

Opioid Rx in USA

Severe Pain is #1 fear in Cancer Patients

https://drugabusestatistics.org/opioid-epidemic/ | https://www.cnn.com/2022/12/14/health/drug-overdose-deaths-slowing/index.html

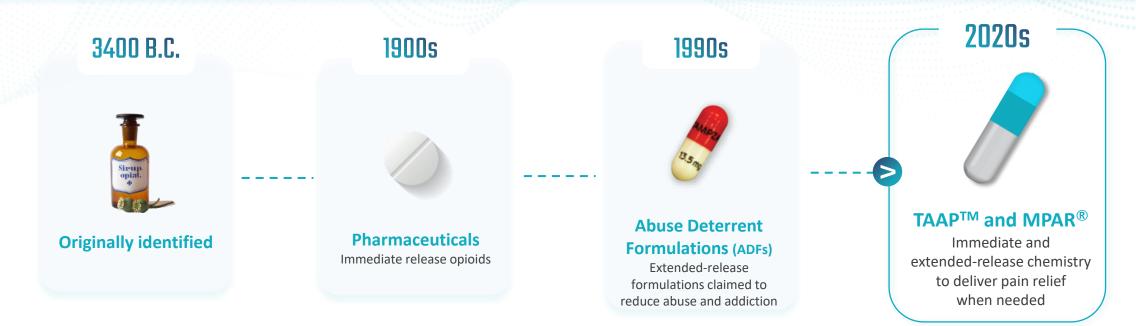


## The Ensysce Solution to Severe Pain

— The Next Generation of Opioids for Powerful Pain Relief

> New class of opioid

> Low abuse – Prescriber confidence/reassurance to patients > Reduced risk of overdose, first time ever





# **Diversified Pipeline**

### **Neuroscience and Respiratory Diseases**

PF614 Pain with abuse protection  TAAP-Oxycodone  PF614-MPAR  Pain with overdose protection  TAAP-MPAR-Oxycodone  PF329  Pain with abuse protection  TAAP-Hydromorphone  PF8001  ADHD - Immediate release  TAAP-Dexamphetamine  PF8026  ADHD - Extended release  TAAP-Dexamphetamine  PF9001  Opioid Use Disorder  TAAP-Methadone	Program	Therapeutic Target	Discovery	Phase 1	Phase 2	Phase 3
PF8001 ADHD - Immediate release TAAP-Dexamphetamine  PF8026 ADHD - Extended release TAAP-Dexamphetamine  PF9001 Opioid Use Disorder TAAP-Methadone	PF614	Pain with abuse protection	TAAP-Oxycodone			
PF8001 ADHD - Immediate release TAAP-Dexamphetamine  PF8026 ADHD - Extended release TAAP-Dexamphetamine  PF9001 Opioid Use Disorder TAAP-Methadone	PF614-MPAR	Pain with overdose protection	TAAP-MPAR-Oxycodo	ne		
PF8026 ADHD - Extended release TAAP-Dexamphetamine  PF9001 Opioid Use Disorder TAAP-Methadone	PF329	Pain with abuse protection	TAAP-Hydromorphone			
PF9001 Opioid Use Disorder TAAP-Methadone	PF8001	ADHD - Immediate release	TAAP-Dexamphetamin	ne		
opicia ose bisoraei	PF8026	ADHD - Extended release	TAAP-Dexamphetamin	е		
	PF9001	Opioid Use Disorder	TAAP-Methadone			
Natamostat* Infectious diseases	Nafamostat*	Infectious diseases				



# Market Opportunity – US

**US Pain Management Drugs Market** 

\$1.1 B

\$2.4 B

**ACUTE** 

**CHRONIC** 

#### — LAUNCH STRATEGY

**Launch PF614** for acute severe pain use

**Launch PF614** for chronic pain use

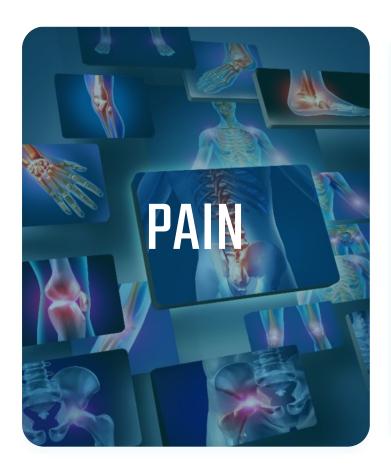
Launch PF614-MPAR for acute/ chronic use

Ref: IQVIA



### PF614 for Severe Pain

— Strong Efficacy – Less Abuse



# **PF614**

- TAAP<sup>™</sup>Prodrug
  - > Delivers potent pain relief equivalent to Oxycontin with reduced abuse potential
- Fast Track granted
- 505(b)(2)
  - > Shortened path to registration





# The Ensysce Difference

PF614
Bioequivalent to OxyContin<sup>1</sup>

1) Clinical support; Potential 505(b)(2) path

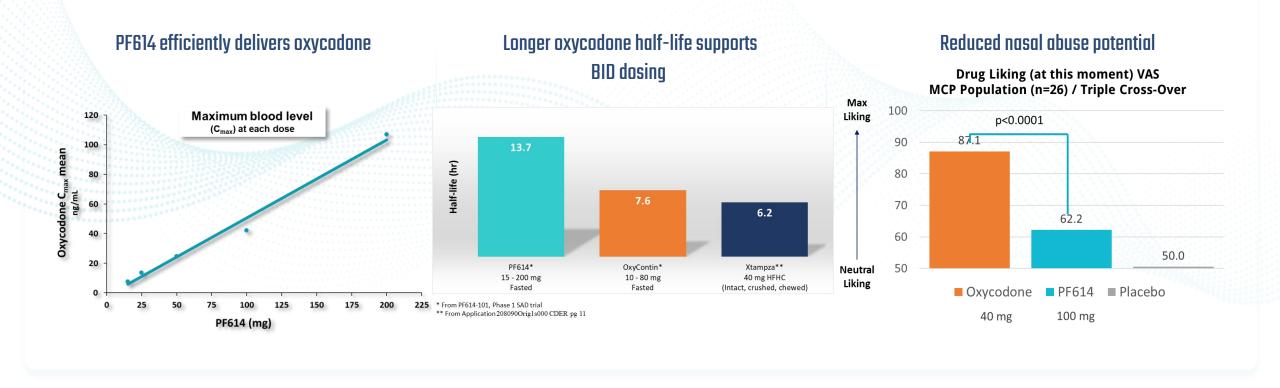
2) Retaining Abuse Deterrence

	PF614	<u>OxyContin</u>	
Efficacy			
Pain Relief (half-life hr)	12.7	7.6	
Safety			
Can dissolve in water <sup>2</sup>		× ×	
Difficult to manipulate		×	
Gnorting/injecting undesirable		×	
Overdose Protection Possible		X	



# PF614 – 12 hour pain relief/reduced abuse

— PF614 Clinical Data





# **Clinical Milestones**



COMPLETED STUDIES 2022-2023	SIGNIFICANCE
PF614-102  Multi-ascending dose and Bioequivalence study  Positive bioequivalence data between PF614 and OxyContin	505(b)(2) Regulatory path possible
PF614-103  Nasal Human Abuse Potential studies:  Significantly Reduced 'Drug Liking' for PF614 vs oxycodone comparator	Abuse-deterrent labeling possible – inhalation
PF614-104  Oral Human Abuse Potential studies:  Significantly Reduced 'Drug Liking' for PF614 vs oxycodone comparator	Abuse-deterrent labeling possible – oral
PF614-201  Efficacy/Time of Onset Study  Time of efficacy onset and pain reduction for 50 and 100 mg PF614	Provides information for Phase 3 study design



# Next Steps for PF614

— Preparation for Phase 3



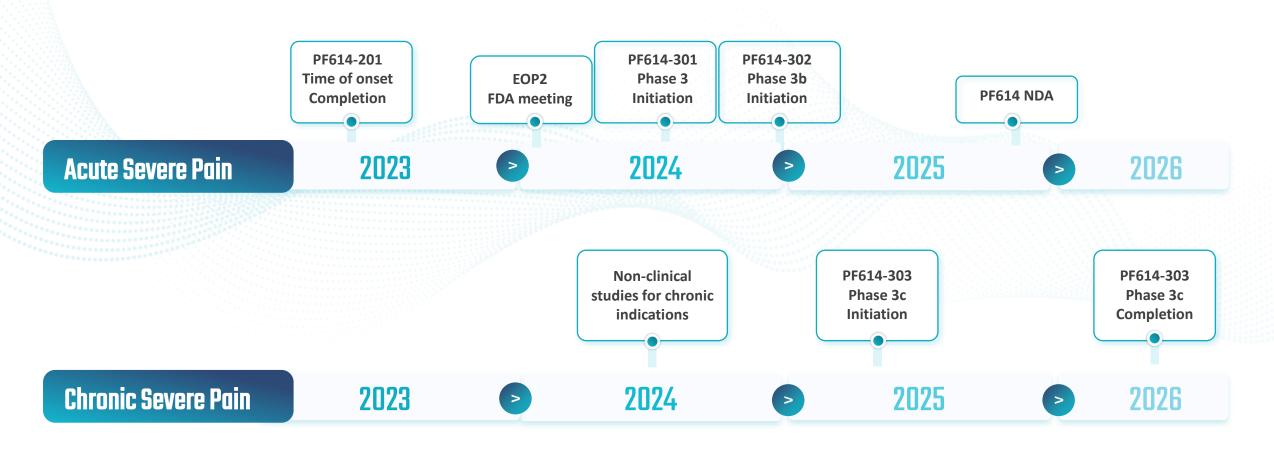
2024	DESCRIPTION	SIGNIFICANCE
Regulatory	End of Phase 2 meeting held to discuss Phase 3 plans for Acute Pain indication	FDA input into non-clinical, CMC and pivotal trials leading to NDA*
PF614-301	Phase 3 study Abdominoplasty: Post-surgical pain	Pivotal study leading to NDA
PF614-302	Phase 3 study Bunionectomy: Post-surgical pain	Pivotal study leading to NDA

<sup>\*</sup>NDA = New Drug Application submitted for approval to the FDA.



### PF614 Development Plans in US

- Development Pathway for Acute and Chronic Pain Indications





### PF614-MPAR

TAAP Oxycodone with overdose protection

**Breakthrough Therapy Designation** Grant by FDA



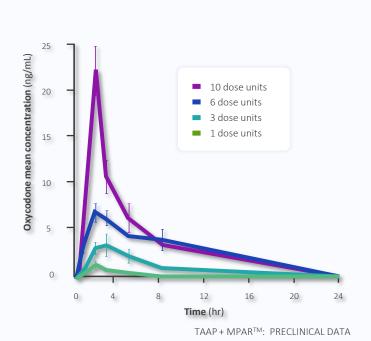


### PF614-MPAR Pre-Clinical Data

Blocks Activation of PF614 and Oxycodone Release if Overdosed

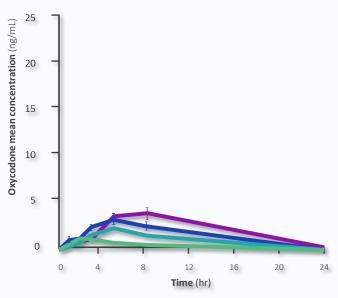
#### Oxycodone levels without MPAR®

PF614 without nafamostat



#### Oxycodone levels with MPAR®

PF614 with nafamostat



in rats n=4 / dose

#### PRE-CLINICAL MPAR SUPPORT DATA

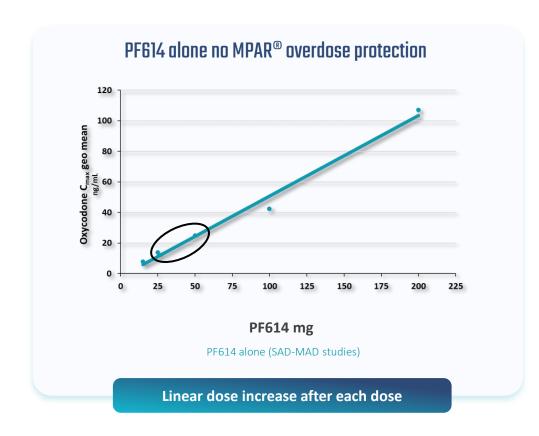
- Combination product of PF614 with an ultrapotent trypsin inhibitor, nafamostat
- Taken at prescribed doses there is no change in oxycodone release from PF614
- With increasing dose unit administration, increasing amounts of nafamostat blocks trypsin release of oxycodone and prevents opioid overdose

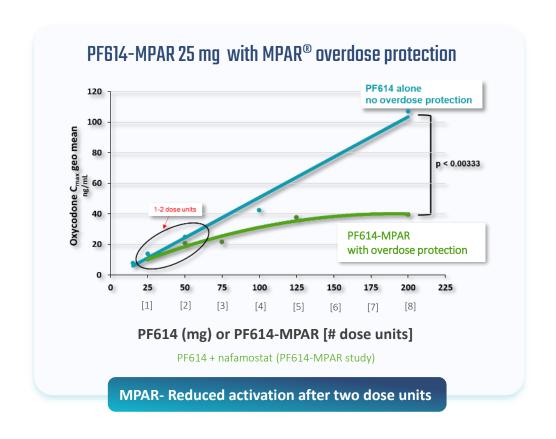




### PF614-MPAR Pain Relief with Overdose Protection

— Phase 1 Clinical Study Demonstrating Overdose Protection





Clinical Milestones



#### **COMPLETED STUDIES 2022-2023**

#### PF614-MPAR-101 Part A:

PF614 and nafamostat

Positive PK data to define drug product

#### PF614-MPAR-101 Part B

Escalating 25 mg PF614-MPAR dose units Confirmation of overdose protection

#### **SIGNIFICANCE**

Identified PF614 / nafamostat combination product for 25 mg dose unit

First demonstration of overdose protection for a prescription opioid

#### PF614-MPAR

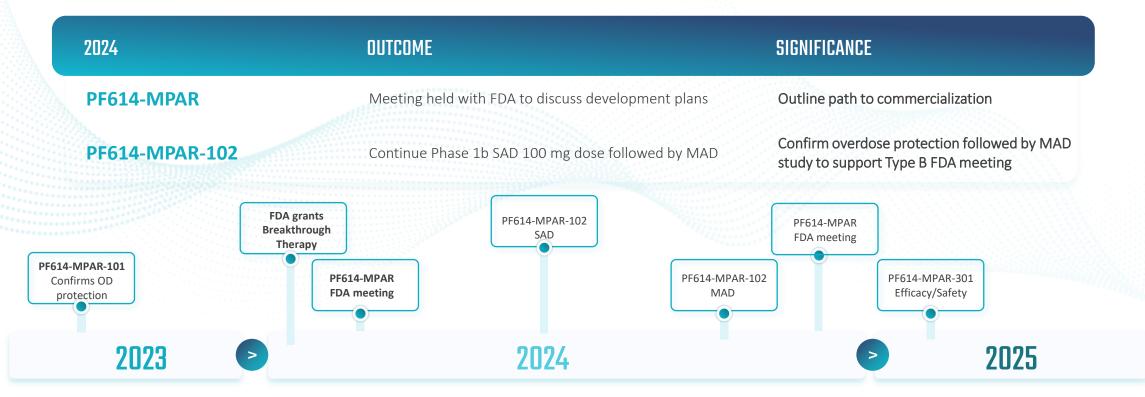
**Breakthrough Therapy Designation** 

Granted by FDA



### PF614-MPAR Development Plans

— Clinical Development for Overdose Protection



**Bold text: Completed** 

Non-bold text: Planned studies

OD: Overdose



# TAAP TM and MPAR®

**Expanded Opportunities** 





# **Drug Development Opportunities with TAAP**<sup>TM</sup>

Improving Drug Delivery and Lifecycle Management

#### TAAP TM CHEMICAL MODIFICATION ATTRIBUTES



Reaches the gastrointestinal tract/epithelial cells intact



Chemistry controlled GI delivery for 'Immediate' or 'Extended-Release'



Improves aqueous solubility

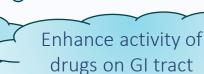


Enhances the drug's permeation through the epithelial lining

#### OPPORTUNITY

0

Our TAAP TM platform enables new chemical entity (NCE) solutions that allow our collaborators to obtain new patents and extend market positions, revitalize approved medications and repurpose approved medications for the benefit of patients and care givers.



Extend half life to improve dosing



Possible oral delivery of injectable drugs



**EXPERIENCED MANAGEMENT** 





### Management Team — Highly Motivated, Experienced Team with Proven Record



#### D. LYNN KIRKPATRICK, PHD

Chief Executive Officer

- Co-founded 2 start up companies
- Developed three targeted small molecule oncology drugs from discovery to clinic
- Experience in private and public company raising funds from private, public and government sources









#### DAVID HUMPHREY, CPA

**Chief Financial Officer** 

- Extensive experience in entrepreneurial environments
- Multiple equity and debt financing, including IPOs
- Focused on financial infrastructure, internal controls with merger and acquisition strategies











#### **GEOFF BIRKETT**

Chief Commercial Officer

- Large pharma leadership experience
- Launched 5 major market-leading brands, including:
  - Nicorette | Prozac | Seroquel | Zomig











#### LINDA PESTANO, PHD

Chief Development Officer

- Experienced in the design of pre-clinical programs focused on building IND-enabling data packages for lead candidate compounds intended for the treatment or diagnosis of cancer and inflammatory diseases
- PhD in Immunology from Tufts, Postdoctoral Research at Dana Farber, Harvard Medical School











#### **WILLIAM K SCHMIDT, PHD**

**Chief Medical Officer** 

- Over 25 years of pharma industry experience, with special emphasis on discovery and development of novel analgesic and narcotic antagonist drugs
- Past President of the Eastern Pain Association, affiliate of the American Pain Society











#### **JEFFREY MILLARD, PHD**

**Chief Operating Officer** 

- Industrial experience in CMC (chemistry, manufacturing, and controls)
- > 7 IND submissions (CDER, CBER, and IMPDs); directed CMC efforts from discovery, in-licensing to commercial launch
- PhD in Pharmaceutical Sciences from University of Arizona











#### **Clinical Advisory Board**

Pain, Addiction and Abuse Expertise



DR. LYNN WEBSTER

Dr. Webster has dedicated more than three decades to becoming an expert in the field of pain management



DR. JEFFREY GUDIN

Dr. Gudin is Faculty Dept of Anesthesiology/Pain Management, Univ of Miami, and Co-Editor of Practical Pain Management.



DR. RICHARD DART

Dr. Dart is the Director of the Rocky Mountain Poison and Drug Center and specializes in emergency medicine and toxicology.



DR. WILLIAM SCHMIDT

Over 25 years of pharma industry experience, with special emphasis on discovery/development of novel analgesic and narcotic antagonist drugs

#### **Board of Directors**

Business, Finance, Healthcare & Regulatory Expertise



Dr. Lynn Kirkpatrick

Career focused on novel drug discovery and development



Dr. Bob Gower

Seasoned Executive and Entrepreneur



**Andrew Benton** 

President Emeritus of Pepperdine University



William Chang

Entrepreneur, Realty Company & Movie executive



Dr. Adam Levin

Academic and clinical orthopedic surgeon at Johns Hopkins Univ.



**Steve Martin** 

Experienced Senior Executive and Chief Financial Officer



Dr. Curtis Rosebraugh

Extensive FDA drug approval experience



Lee Rauch

Experienced CEO and Strategy Advisor



### Cash Resources

NASDAQ: ENSC

**Shares Outstanding** Shares Public Float

7.3M

As of March 8, 2024

7.2M

Nasdaq Listed

July 2021

Headquarters

La Jolla, CA

\$1.1M Cash as of 12/31/23

**Grant Funding** Available

as of 12/31/23

\$2.1M

Warrant **Exercises** January 2024

**Financing Gross Proceeds** February 2024



### **NIH** support

2018-2023

Ensysce received \$11M+ to advance MPAR®

Four-year award received to undertake the development of the overdose protection platform MPAR® (Multi-Pill Abuse Resistance).



### **NIDA** grant

2019-2024

NIDA awarded Ensysce up to \$15M grant to advance TAAP/MPAR® for OUD

Five-year award to undertake the preclinical and clinical development of TAAP and MPAR® for treatments of Opioid Use Disorder.



### **Ensysce Summary**



**Clinical-stage company** - transformative trypsin-controlled chemistry.



Targeted therapy areas focus on products with blockbuster potential.



**Lead Product with demonstrated efficacy, reduced clinical risk,** and positive data showing **reduced abuse potential.** 



**Shortened development timeline** with Fast Track and 505(b)(2) regulatory pathway, **de-risked** with **positive clinical data** showing the technology works.



**Strong global patent estate** 



**Highly experienced management team -** broad biopharma background, from drug development to commercialization.



TAAPTM
Anti-abuse chemistry



MPAR®
Overdose protection



### **Investor Relations**

#### **SHANNON DEVINE**

MZ North America

203-741-8811

ENSC@mzgroup.us

7946 Ivanhoe Avenue, Ste 201, La Jolla, CA 92037

WWW.ENSYSCE.COM









 $Ensysce^{^{\text{\tiny TM}}}$ **APPENDIX** 



# Pain Relief Delivery by TAAP

— Two-Step Release Process



#### CHEMICAL MODIFICATION

Allowing either immediate or extended release



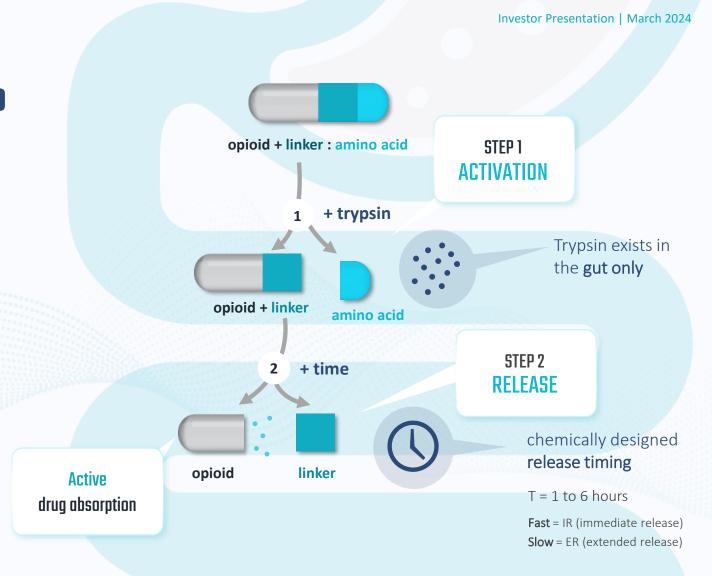
#### **ONLY ACTIVATED BY TRYPSIN**

Opioid not released by chewing, injecting or snorting



#### NOT ALTERED BY MANIPULATION

Difficult to extract opioid



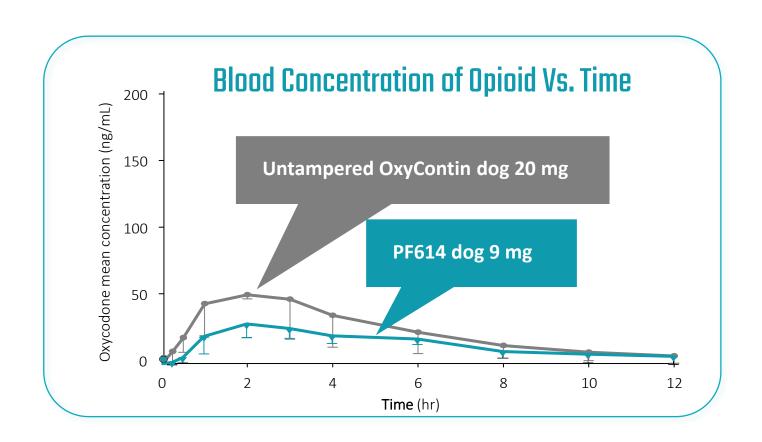


# **PPF614 Delivery Profile**

Equivalent to OxyContin

#### TAAP™ Preclinical Data

- > PF614 chemically releases oxycodone with the same extended release (ER) profile as OxyContin
- The same release profile demonstrates that PF614 will achieve similar pain relief as OxyContin



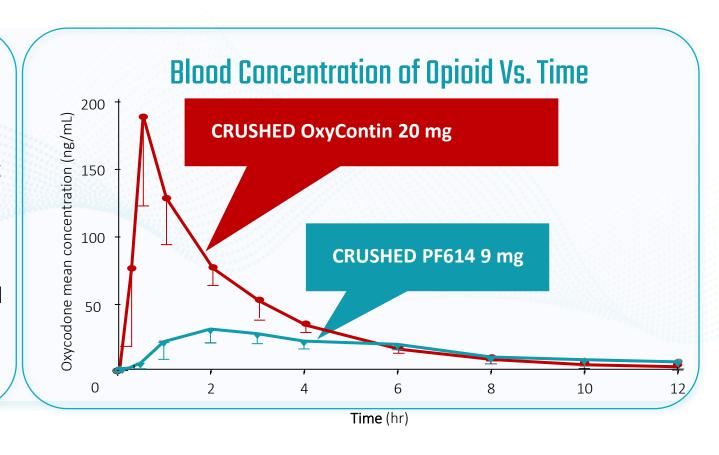


### PF614 Cannot be Manipulated to Change Delivery

— PF614 Release Profile Does Not Change

#### TAAP™ Preclinical Data

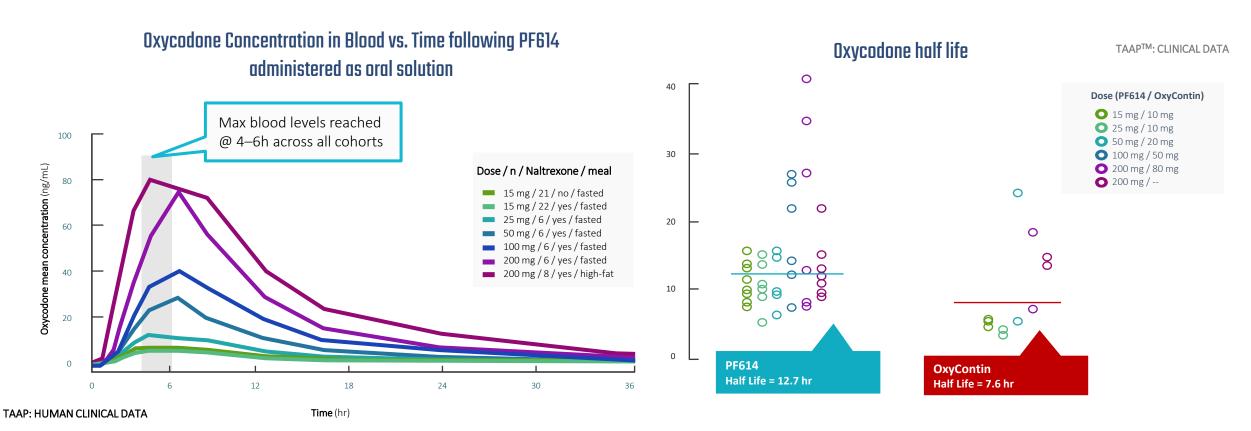
- > PF614, even when crushed, releases oxycodone slowly in the blood, thereby reducing the large Cmax which leads to reduced 'drug liking'.
- > The study demonstrated the significant difference between the manipulated PF614 versus manipulated (crushed) OxyContin





# PF614 Designed with Longer-Lasting Pain Relief

— PF614-101 Clinical Data



PF614 provides good safety profile, efficient conversion to oxycodone and longer half-life than OxyContin.



# PF614 Efficiently Delivers Oxycodone

#### — Efficiently Delivers

#### PF614

Delivers oxycodone efficiently

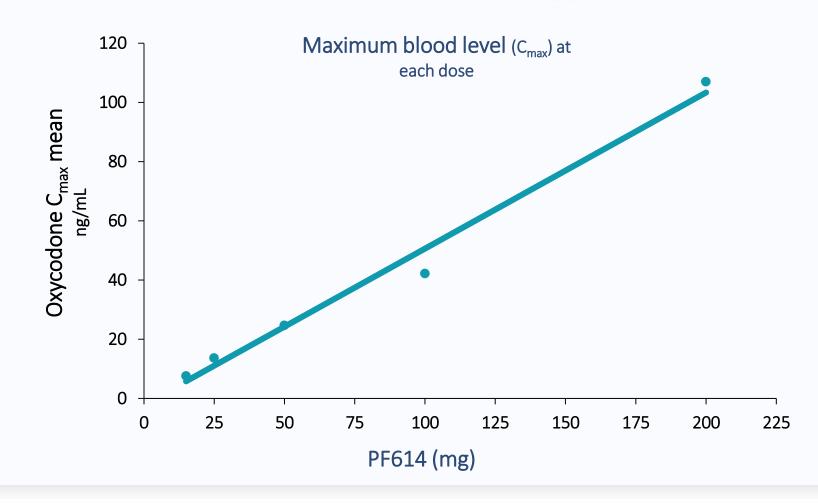
Delivers oxycodone in dose dependent fashion.

Delivers oxycodone with reduced abuse potential

#### Dose levels

**PF614\*:** 15, 25 mg n= 6/dose

**PF614\*\*:** 50, 100, 200 mg: n=6/dose



<sup>\*</sup> From SAD Study PF614-101

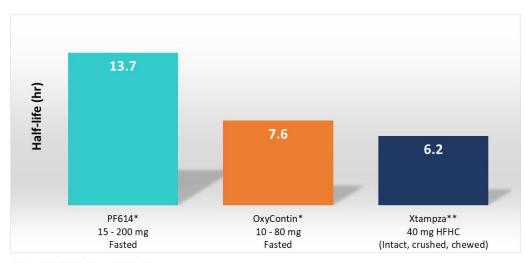
<sup>\*\*</sup> From MAD Study PF614-102



# PF614 delivers oxycodone in a clinically advantageous way

- PF614 is expected to deliver a full 12 hours of pain relief in more patients than OxyContin

### Average Oxycodone half-life after a dose of PF614 supports BID dosing



<sup>\*</sup> From PF614-101, Phase 1 SAD trial

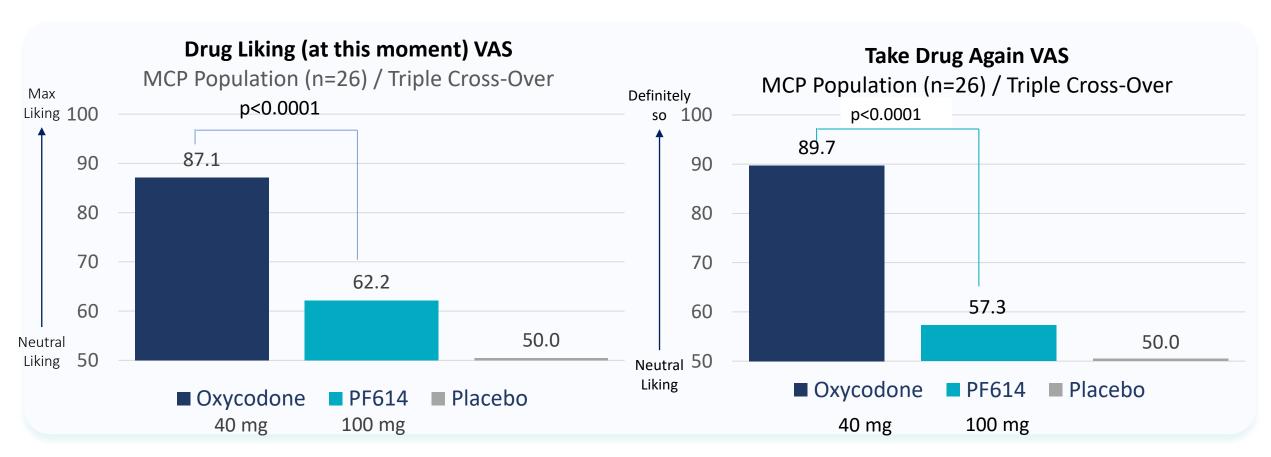
- A half-life of over 13 hours for the oxycodone from each PF614 dose suggests continuous activity will result from BID dosing in a high majority of patients
- This could translate to less day and night breakthrough pain, fewer patients enduring a cycle of twice daily withdrawals, and reduced need more frequent or higher doses over time
- OxyContin was only administered BID in Phase 3 clinical trials and approved as such by FDA, yet its average half-life is well short of 12 hours, suggesting that BID dosing could be inadequate for many patients

<sup>\*\*</sup> From Application 208090Orig1s000 CDER pg 11



# PF614 Displays Significantly Reduced Drug Liking

— PF614-103 Nasal Human Abuse Potential Study





## PF614-102 MAD/BE

— Multi-Ascending Dose / Bioequivalence Study

A Phase 1b, Randomized, 2-Part Single-Center Study to Evaluate the Pharmacokinetics and Safety of Multiple-Ascending Oral Doses of PF614 and the Food Effect and Bioavailability/Bioequivalence of Single Oral Doses of PF614 Relative to OxyContin in Healthy Adult Subjects

#### The primary objectives of the study were:

To assess the safety, tolerability and pharmacokinetics of intact prodrug, PF614, in comparison to OxyContin.

#### Administration

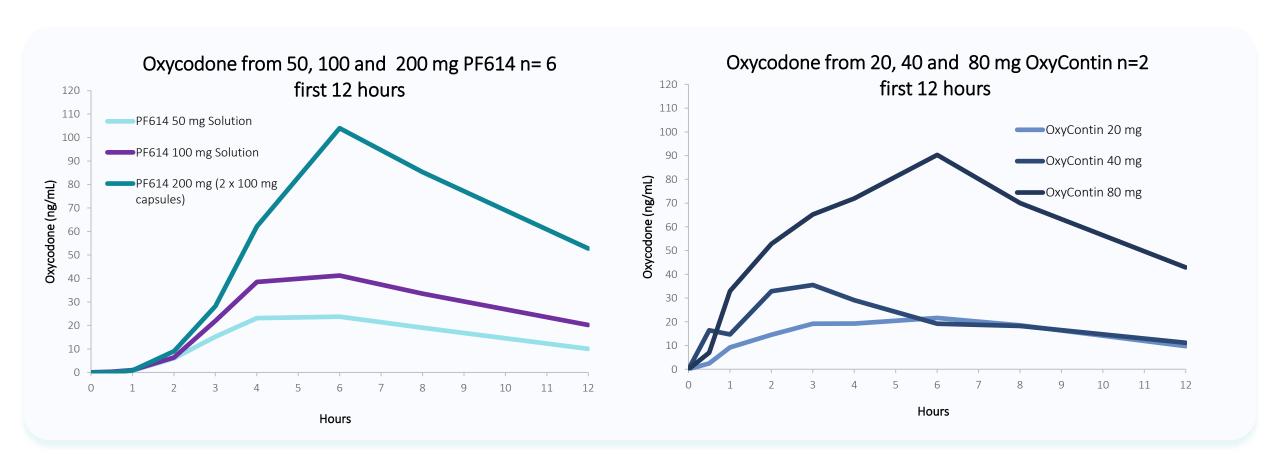
MAD: Oral twice daily (BID) doses for 5 days to groups of healthy adult subjects, naltrexone blocked randomized 3:1 PF614 to OxyContin. N=24

**BE:** Single oral dose of PF614 100 mg or OxyContin 40 mg under fasted and fed (high fat meal) conditions. N=60 to complete 4 conditions.



### PF614-102 MAD

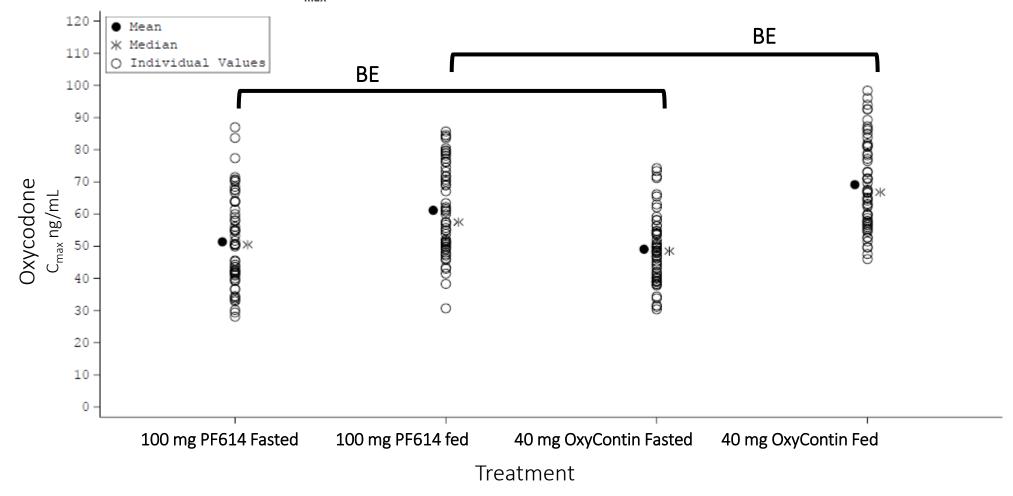
— Pharmacokinetics (PK): oxycodone release from PF614 or OxyContin





### PF614-102 BE

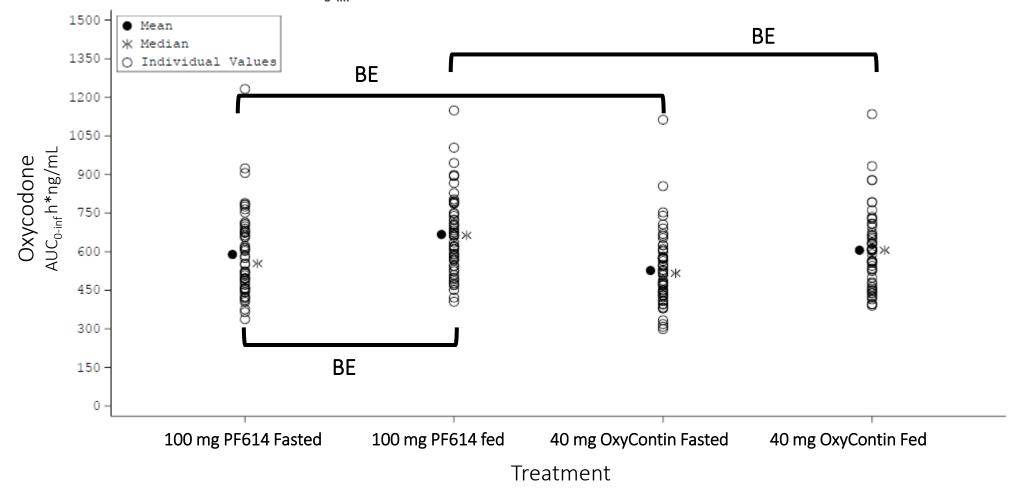
PK: Oxycodone from OxyContin or PF614 C<sub>max</sub> Fasted or Fed





### PF614-102 BE

PK: Oxycodone from OxyContin or PF614 AUC<sub>0-inf</sub> Fasted or Fed





### PF614-102

#### SAFETY: PF614 and OxyContin produce similar Adverse Events

#### Part A: Table of Adverse Events

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

#### Part B: Table of Adverse Events

	PF614 fasted	OxyContin fasted	PF614 fed	OxyContin fed
	100 mg	40 mg	100 mg	40 mg
	n=58 n (%)	n=59 n (%)	n=58 n (%)	n=58 n (%)
Total subjects with at	14 (24.1)	12 (20.3)	12 (20.7)	9 (15.5)

<sup>\*</sup> Treatment Emergent Adverse Events: Vertigo, Photophobia, Nausea, Constipation, Diarrhea, Vomiting Urinary Tract infection, Tooth fracture, Decreased appetite, Dizziness, Headache, Depressed mood, Rhinorrhoea, Dermatitis, fall



PF614-MPAR®

Data Updates





### MPAR® Mechanism of Action

Combination Product With Dose-Triggered Overdose Protection

MPAR® Combination Product Legend:





TAAP-enabled opioid

PRESCRIBED DOSE

**Delivers pain** relief as needed







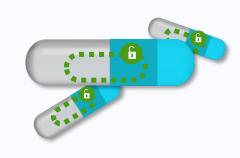
DOSE THRESHOLD

**Trypsin activation** releases free and active drug product





**EXCESS DOSE** 



#### **ACCIDENTAL OVERDOSE**

MPAR® begins to inhibit trypsin, 'turning off' activation of TAAP and limiting opioid release.





#### **EXCESS MPAR DOSE**

Trypsin Activation **blocked** / overdose **averted** 

 $\mathsf{MPAR}^{^{\textcircled{R}}}$  is only triggered by an overdose



### PF614-MPAR-101

— MPAR CLINICAL DATA: PF614 (25 mg) with and without nafamostat (10 mg)

A Single Dose Study to Evaluate the Pharmacokinetics of Oxycodone and PF614 when PF614 Solution is Co Administered with Nafamostat, as an Immediate Release Solution and/or Extended Release (ER) Capsule Formulations in Healthy Subjects

#### The primary objectives of the study are:

To assess the pharmacokinetics (PK) of oxycodone, when PF614 solution is administered alone and with nafamostat as an immediate-release (IR) solution and/or extended-release (ER) capsule prototypes

#### Administration

Single oral dose of PF614 (25 mg) with or without nafamostat IR/ER or a combination (10 mg total) to groups of healthy adult subjects

#### Cohort 1

**PF614** 25 mg n = 8

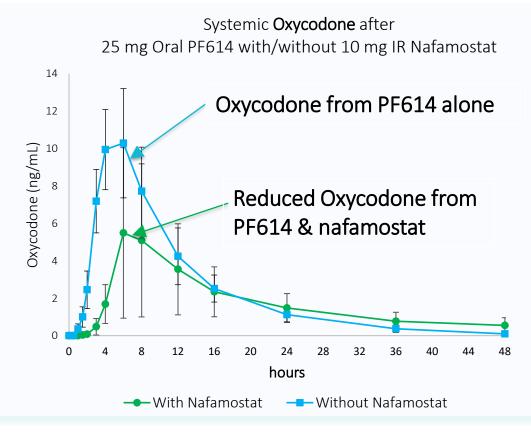
**PF614** 25 mg and **nafamostat** 10 mg n = 6

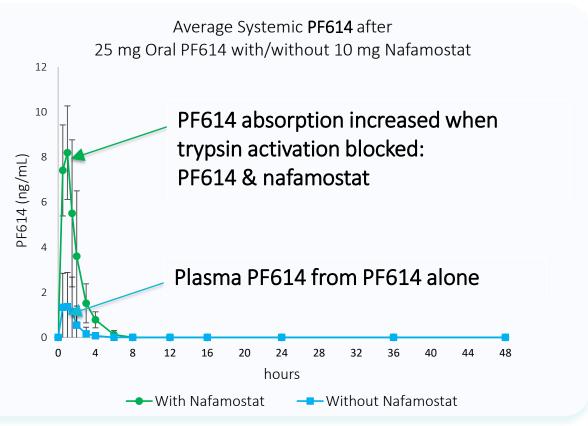


### PF614-MPAR-101 Part A

— PF614 (25 mg) with and without IR nafamostat (10 mg)

#### First Demonstration of Human Overdose Protection:



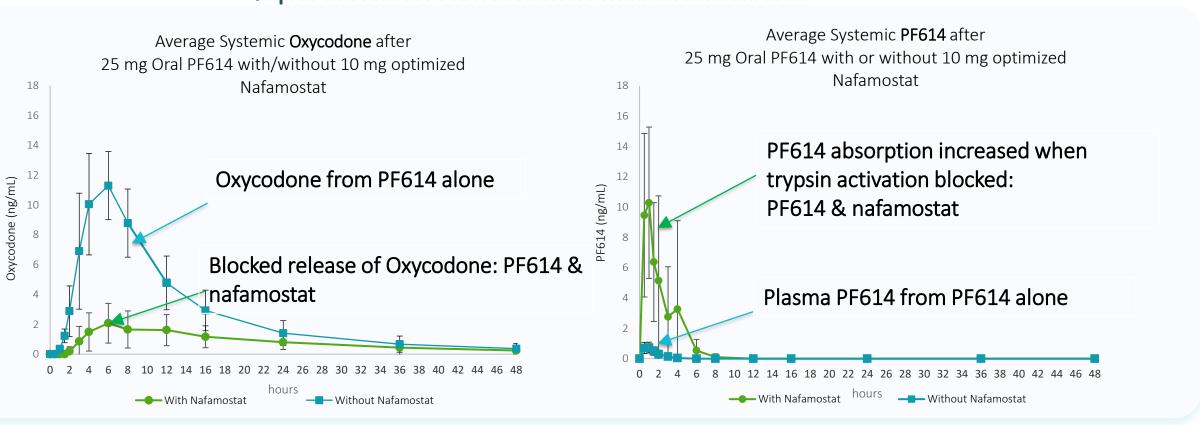




### PF614-MPAR-101 Part A

—— PF614 (25 mg) with and without formulated nafamostat (10 mg)

#### **Improved Overdose Protection with Formulated Nafamostat:**





### PF614-MPAR Pain Relief with Overdose Protection

Phase 1 study Part B Demonstrating Overdose Protection

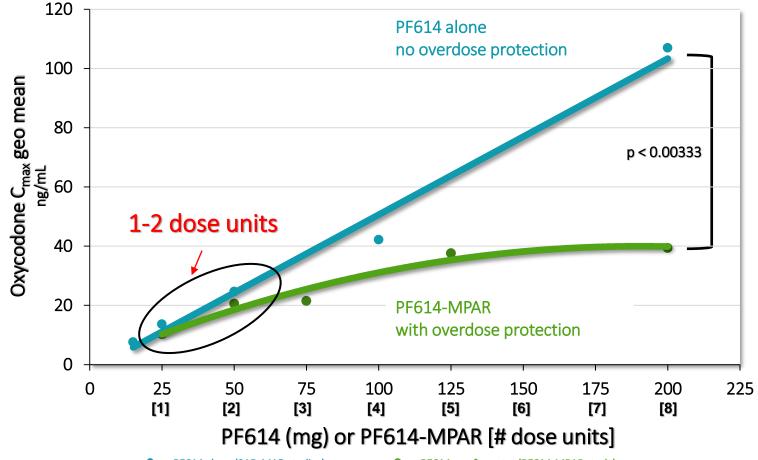
#### Target Product Profile: PF614-MPAR

- To deliver oxycodone in a prescribed dose up to 2 PF614-MPAR capsules (black oval) without change in systemic oxycodone delivery compared to PF614 alone (blue line).
- To reduce oxycodone delivery when 3 or more capsules are consumed simultaneously (overdose) as reflected by suppression of C<sub>max</sub> (green line).

**PF614-MPAR** 25 mg PF614 = 1 dose unit (1, 2, 3, 5, and 8 capsules): n=12/dose

**PF614\*:** 15, 25 mg n= 6/dose

**PF614\*\*:** 50, 100, 200 mg: n=6/dose



<sup>\*</sup> From SAD Study PF614-101

<sup>\*\*</sup> From MAD Study PF614-102