W0930-12-79

Development of an extended release nafamostat formulation for prescription drug overdose protection

D. Lynn Kirkpatrick[1], Jeff Millard[1], Linda A. Pestano[1], William K. Schmidt[1], Cari Evans[1], Vanessa Zann[2], Wu Lin[2], Jefferey Levy[2], Katie Pepper[2], Dolly Jacob[2]

1. Ensysce Biosciences, La Jolla, CA, US
2. Quotient Sciences, Nottingham, UK

CONTACT INFORMATION: info@quotientsciences.com

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PURPOSE

- Prescription opioid abuse and overdose are major society burdens, resulting in significant costs, illnesses, and deaths.
- PF614, an oxycodone-derived prodrug, was designed to reduce abuse as it requires exposure to trypsin in the small intestine to release oxycodone. Injection, insufflation, plugging, and dose dumping are not possible means of abuse of PF-614 due to its molecular design.
- MPAR® (Figure 1) is a combination of Trypsin Activation Abuse Protection (TAAP™) (Figure 2) prodrug platform (PF614) and a protease inhibitor (nafamostat) that provides overdose protection at a molecular level.
- The short half-life of nafamostat required development of an extended release (ER) formulation to ensure trypsin inhibition is maintained for the duration that PF614 prodrug is transiting the small intestine.
- Optimization of the PF614-MPAR formulation with evaluation of several variables including ER nafamostat release rate (modified by bead coating), ER and immediate release (IR) nafamostat dose ratio, and PF614:nafamostat dose ratio, is described.

Figure 1: MPAR SMART overdose protection

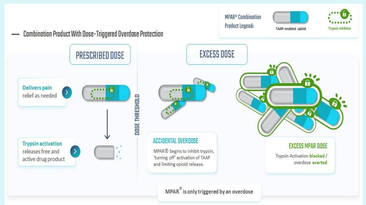
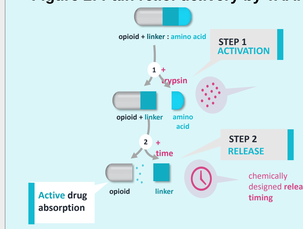


Figure 2: Pain relief delivery by TAAP



OBJECTIVES

Overall Aim

Identify a unit dose of nafamostat (IR and/or ER) which didn't impact oxycodone release from PF614 when the prescribed dose was ingested (1 or 2 units) but would inhibit PF614 activation, and consequent oxycodone exposure, in an overdose situation (3 or more units).

Part 1 – Formulation Optimization Part

- To assess the pharmacokinetics (PK) of oxycodone and PF614 when PF614 is administered alone or with nafamostat as an IR solution and/or ER capsule prototypes
- To provide safety and tolerability information for PF614 when administered alone or in combination with IR and ER nafamostat

Part 2 – Simulation of overdose situation

- To assess the effect of the selected nafamostat formulation (IR and or ER) on the PK of oxycodone at multiple dose levels (once a day [QD] and twice a day [BID])
- To provide safety and tolerability at increasing unit dose levels of both the selected nafamostat formulation and PF614

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METHODS

Translational Pharmaceutics® Platform integrates drug substance, formulation development, GMP manufacturing and clinical dosing activities within a single provider and provides significant acceleration to early development programs. When applied in drug product optimization, Translational Pharmaceutics allows the assessment of multiple formulation technologies or formulation prototypes during a clinical study. Small batches are manufactured just prior to dosing, saving time in formulation scale up and stability data generation. Interim data reviews after each dosing period assess safety, tolerability and PK to determine the next technology or prototype to be manufactured and evaluated, typically on a 2-3 week cycle time. The ability to assess different formulation prototypes within a clinical program allows formulation optimization which maximizes the potential for clinical success (1).

The clinical study was a 2-part, randomized, open-label study.

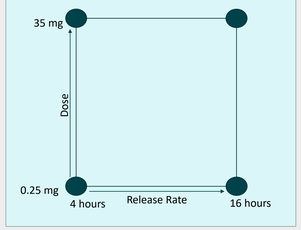
- Part A was a formulation optimization study for the nafamostat formulation (IR solution and/or ER prototype capsules).
- Part B assessed PF614 25 mg combined with the formulated nafamostat prototype selected from Part A, in increasing dose units from 1 to 8 capsules administered simultaneously to simulate opioid overdose in naltrexone-blocked healthy volunteers. Part B also assessed twice a day dosing with the selected formulation in healthy subjects.

Interim decisions occurred between dosing periods, whereby PK and safety, were reviewed to decide on formulation selection (nafamostat dose and ER/IR combination) for future dosing periods.

Formulation Design Space

- 2-dimensional (2D) design space for the ER beads (Figure 3), varying both nafamostat dose and release rate, was combined with a dose bracket for the IR nafamostat solution, allowing 3 variables to be changed within the clinical study.
- Nafamostat ER beads were developed using methacrylate copolymers with release rates targeting a cumulative 90% release in 4 to 16 hours and a dose range of 0.25 mg to 35 mg, with a maximum dose used clinically of 10 mg.
- ER beads were filled into capsules for dosing and were co-administered with PF614 and nafamostat IR oral solutions.

Figure 3: 2D design space for nafamostat ER beads

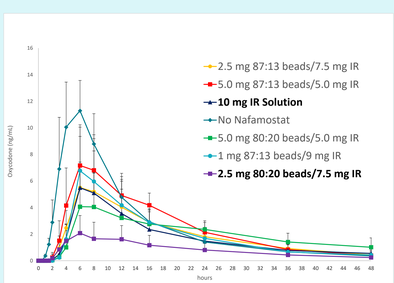


RESULTS

Part A – Formulation Optimization Part

- 11 cohorts of 6 or 8 healthy volunteers were dosed with PF614 25 mg alone or with various IR/ER nafamostat combinations in Part A.
- 10 different formulation combinations, 25 mg PF614 with 0 to 10 mg nafamostat (IR and /or ER) were assessed in Part A.
- ER nafamostat beads with release rates of 90% at 9 hours (slow) or 90% at 6 hours (fast) were evaluated and the effect of 1 to 10 mg nafamostat (IR and ER combination) on oxycodone release was assessed.
- Oxycodone exposure was reduced in the presence of nafamostat due to trypsin inhibition preventing the conversion of PF614 into oxycodone (Figure 4 and 5).
- Oxycodone exposure was modified by varying release rate of the ER nafamostat bead and the IR/ER ratio.
- A nafamostat formulation with the optimal ER release rate, ratio of IR and ER nafamostat, and total dose for the PF614-MPAR 25 mg dose unit was identified in Part A.

Figure 4: Oxycodone plasma concentration time profiles following administration of 25 mg PF614 and various nafamostat (IR/ER) formulation combinations



RESULTS

Part B –Simulation of overdose situation

- The optimized formulation identified in Part A was 25 mg PF614 IR solution formulation administered with 1 mg formulated nafamostat (IR/ER combination), this is 1 unit dose.
- 1 cohort of 12 subjects received 7 sequential dosing periods where subjects received increasing unit dose levels after appropriate washout period.
- Part A data (Figure 5) demonstrated that increasing unit doses of nafamostat (e.g. 1,3 and 10 dose units) decreased oxycodone exposure.
- Overdose situation was assessed in Part B by measuring oxycodone exposure after 1, 2-, 3-, 5- or 8-unit doses administered simultaneously.
- Exposure of oxycodone with 1 or 2 dose units produced plasma levels similar to doses of PF614 25 mg or 50 mg alone, showing that the addition of nafamostat had no effect on PF614 conversion to oxycodone.
- Administration of 3 units or greater, oxycodone plasma levels were reduced compared to PF614 alone at the same dose levels in prior single and multiple ascending dose (MAD) studies, confirming inhibition of PF614 conversion to oxycodone (Figure 6).

Figure 5: Oxycodone plasma concentration time profiles following administration of PF614 25 mg alone or with 1, 3 and 10 dose units of Nafamostat ER/IR 1 mg

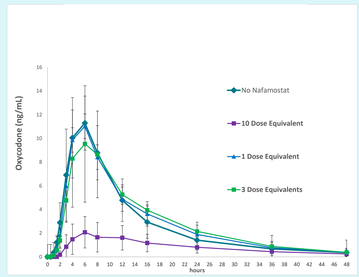
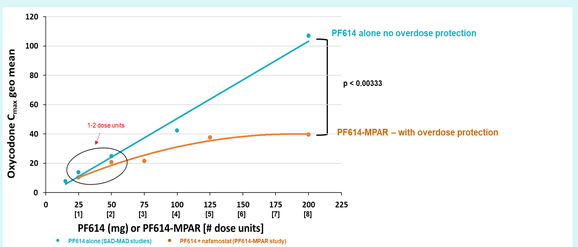


Figure 6: Oxycodone C_{max} levels when administered with increasing unit dose levels or PF614 alone or PF614 and nafamostat IR/ER formulation



CONCLUSIONS

- A PF614-MPAR (25 mg) single unit dose that delivered oxycodone at a prescribed plasma level equivalent to 10 mg oxycodone HCl but prevented oral overdose when consumed in excess was identified.
- A proof-of-concept arm, dosing increasing unit doses of PF614 combined with formulated nafamostat (PF614-MPAR), provided evidence that MPAR effectively attenuated oxycodone levels at up to 8x higher dose levels compared to PF614 alone, supporting its provision of overdose protection.
- **PF614-MPAR could be the first opioid product with *abuse resistance* and *overdose protection.***

REFERENCES

1. DiMasi, J.A., Wilkinson, M. *Ther Innov Regul Sci* **54**, 1453–1460 (2020).