Poster 244

Fentanyl Pectin Nasal Spray (FPNS) With PecSys®: Onset of Action, Consistency, and Acceptability in Breakthrough Cancer Pain (BTCP)

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INTRODUCTION

- Breakthrough cancer pain (BTCP) is defined as a transitory exacerbation of pain that occurs on a background of otherwise controlled persistent pain using opioids.[1]
- BTCP affects 60%–95% of all cancer patients with pain.[1-3] This distinct component of cancer pain may have a significant negative impact on patient quality of life and personal relationships,[3] and may increase health care costs.[4]
- Although BTCP is highly variable, a typical BTCP episode is rapid in onset (median onset to peak pain intensity [PI] ~3 minutes) and short-lived (median 30 minutes).[1]
- BTCP is typically treated with oral opioids, such as oral morphine or oxycodone. The time to peak effect for such formulations can be too slow to be consistent with the profile of the typical BTCP episode.
- Treatment of BTCP may yield improved outcomes if the time course of pain relief (PR) were to correspond more closely to the typical time course of the pain than is possible with oral opioids.[5]
- Consistent efficacy, ease of use, convenience and patient acceptability are factors to consider in optimising management of BTCP.
- The nasal route of administration has the potential for rapid drug delivery, and is safe and convenient for most patients. Fentanyl is a well-established, effective, opioid analgesic with lipophilic properties that may make it highly suitable for nasal administration.
- Recently, a fentanyl pectin nasal spray (FPNS) has been developed to optimise the absorption profile of fentanyl across the nasal mucosa. The PecSys® delivery platform allows fentanyl to be delivered gently in a low-volume, fine mist of uniform droplets. When sprayed into the nasal passage, the pectin forms a thin layer of gel on contact with calcium cations found in the nasal mucosal fluid. This formulation produces a rapid controlled delivery of fentanyl with pharmacokinetics that approximate the time course of a typical BTCP episode.
- The primary objective of this study was to demonstrate the efficacy of FPNS in the treatment of BTCP in opioid-tolerant patients who are receiving regular opioid therapy; secondary objectives were to demonstrate the onset of action, time to clinically meaningful PR, safety, tolerability and acceptability of FPNS.

METHODS

Study Design

- Multicentre (N=38), randomised, placebo-controlled, double-blind, crossover study conducted in the United States, Argentina and Costa Rica
- This study protocol was executed in accordance with regulatory and good practice guidelines (e.g., International Conference on Harmonisation [ICH] E6 = Good Clinical Practice [GCP] and the Code of Federal Regulations).
- The four-phase study design included a screening phase (up to 10 days), an open dose-titration phase (maximum of 14 days), a double-blind treatment phase (3–21 days) and an end-of-treatment phase (1–14 days following last dose).
- Patients had to complete the dose-titration phase (titration to an effective dose that successfully treated 2 consecutive episodes of target BTCP without unacceptable adverse events) to be eligible to continue to the double-blind, placebo-controlled, crossover phase in which up to 10 BTCP episodes were treated with study medication.
- The maximum study duration for individual patients was set at 6–8 weeks.

Patients

- Male or female patients, aged 18 years and older, with a malignancy who were taking regular, around-the-clock medication (60 mg oral morphine or equivalent opioid) for their underlying persistent cancer pain and who typically had 1–4 episodes of BTCP per day were eligible for participation.
- Main exclusion criteria included patients with uncontrolled or rapidly escalating pain or whose condition was deemed unstable or rapidly deteriorating. Patients with a medical condition (i.e., respiratory, cardiac, hepatic or renal, neurological, psychiatric) that would make them unsuitable for the study, a history of alcohol or substance abuse, or radiotherapy within the previous 30 days were also excluded. Additionally, patients with any abnormal nasal physiology and/or pathology or taking any medications likely to affect the physiology of the nasal mucosa were not eligible.

Study Medication

- *Titration phase:* FPNS 100–800 µg (1–2 sprays, depending on selected dose) per episode of target BTCP up to a maximum of 4 total doses per day
- *Double-blind phase:* 10 total doses: 7 doses of FPNS 100, 200, 400 or 800 µg and 3 doses of placebo. Treatment per episode of target BTCP up to a maximum of 4 total doses per day

Assessments and Outcome Measures

- Electronic diaries (e-diaries) were used to collect efficacy assessments and outcomes measures. Validated instruments were used to assess efficacy and outcomes.
- Efficacy for each dose of blinded study medication was assessed by the patient, who recorded (using an e-diary) PI and PR for each episode of breakthrough pain treated. Assessments were made before taking study drug (baseline score) and 5, 10, 15, 30, 45 and 60 minutes after dosing.
- PI was assessed using an 11-point numerical scale (0 = no pain to 10 = worst possible pain); PR was assessed using a 5-point scale (0 = none to 4 = complete).
- For each episode, use of rescue medications was recorded (yes or no), and patient acceptability assessments (4-point Likert scale; 1 = not satisfied to 4 = satisfied) were made at 30 and 60 minutes post dose.
- After the last treated episode of BTCP in the double-blind phase, patients were also asked to rate overall satisfaction with the ease of use and convenience of FPNS.

Tolerability

- Adverse events were recorded throughout the study.
- Objective nasal assessments were performed by the study physician at screening and at the end of treatment.
- A Nasal Symptom Score was completed by patients at 30 and 60 minutes following dosing for each episode during the double-blind period. They rated their experience with 10 adverse symptoms—stuffy nose, runny nose, itching or sneezing, crusting or dryness, burning or discomfort, bleeding, cough, postnasal drip, sore throat, taste disturbance—using a 4-point scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe).

Statistical Analysis

- *Modified intent-to-treat (ITT) analysis set:* all patients in the randomised population who had treated at least 2 episodes (1 with each of the 2 study medications) and for which at least 1 post-baseline PI measurement was available
- *Safety analysis set:* all patients who received at least one dose of FPNS
- Analyses of the effects of FPNS on BTCP episodes in this study included:
  - Number and percentage of all total treated episodes in each treatment group with a reduction in PI score of ≥1 at 5, 10, 15, 30, 45, 60 minutes
  - Number and percentage of total treated episodes in which a clinically meaningful (defined as ≥2-point change) reduction in PI score from baseline was observed at 5, 10, 15, 30, 45 and 60 minutes
- All evaluable episodes were considered in the analyses (up to 7 during FPNS exposure and up to 3 during placebo exposure). Incidences were based on total number of evaluable episodes, regardless of how many episodes were experienced by each patient.
- For the acceptability assessments, responses were averaged across episodes to derive the average scores for each question for a patient. This was then used to derive the average patient score for each question for each treatment group.
- The last-observation-carried-forward (LOCF) method was used to input missing scores for evaluable episodes due to omission or use of rescue medication.
- Clinical endpoints were analysed using an analysis of covariance (ANCOVA) with Statistical Analysis Software (SAS).

RESULTS

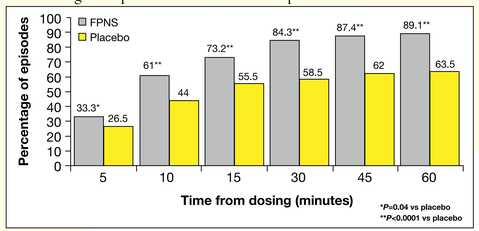
Study Disposition and Baseline Demographics

- Overall, 72.8% of patients who entered the dose-titration phase were randomised to double-blind treatment. Of the patients who withdrew from the titration phase, only 6% withdrew due to lack of efficacy; 5% withdrew due to adverse events.
- Of the 83 patients randomised, 76 (91%) completed the study and 87% elected to continue treatment post study.
- A total of 659 BTCP episodes were analysed (FPNS N=459; placebo N=200).
- Of the 83 patients randomised to the double-blind phase, 73 patients were included in the modified ITT population: 100 µg: n=8; 200 µg: n=7; 400 µg: n=24; 800 µg: n=34.
- The mean age at baseline was 53.8 ± 11.6; 72.6% of patients were aged ≤60 years. Overall, 53.1% of patients were male; 68.1% of patients were Caucasian, 11.5% were Black, 1.8% were Asian, and the rest were classified as being of other origin.

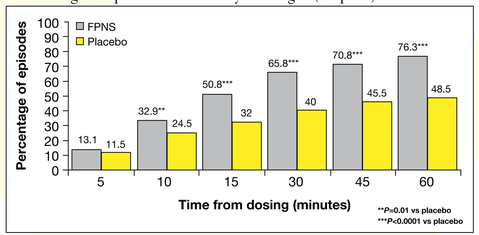
Pain Intensity

- **Figure 1** shows that, compared with placebo, 33% of FPNS-treated episodes showed onset of PI improvement (1-point reduction in PI) at 5 minutes ($P<0.05$), 61% at 10 minutes and 73% at 15 minutes (both $P<0.0001$).
- **Figure 2** shows that compared with placebo, 33% of FPNS-treated episodes had a clinically meaningful (≥2-point) reduction in PI ($P<0.01$), 66% at 30 minutes ($P<0.0001$).

1. Percentages of episodes with onset of PI improvement.



2. Percentages of episodes with clinically meaningful (≥2-point) reduction in PI.



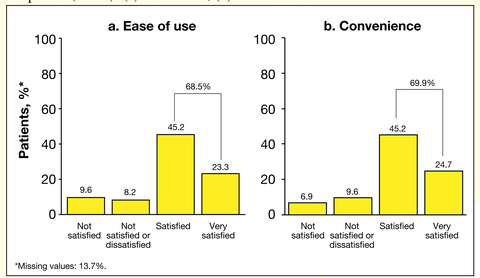
Rescue Medication

- Overall, 90.6% (416 of 459) of episodes of BTCP treated with FPNS versus 80.0% (160 of 200) of episodes treated with placebo did not require additional rescue medication within 60 minutes ($P<0.001$).

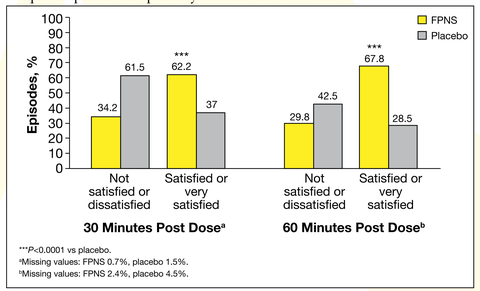
Patient Acceptability

- **Figure 3** shows that overall, the majority of patients were satisfied (satisfied/very satisfied) with the convenience and ease of use of a nasal spray.
- **Figure 4** shows that at 30 minutes post dose, satisfaction (satisfied/very satisfied) was reported in 62% of episodes treated with FPNS versus 37% treated with placebo ($P<0.0001$). Similarly, at 60 minutes post dose, satisfaction was reported in 68% of episodes treated with FPNS versus 38% treated with placebo ($P<0.0001$).
- 87% of patients elected to continue treatment with FPNS at the end of the study.

3. Overall patient acceptability assessments of a nasal spray after last treated episode (n=73): (a) ease of use; (b) convenience.



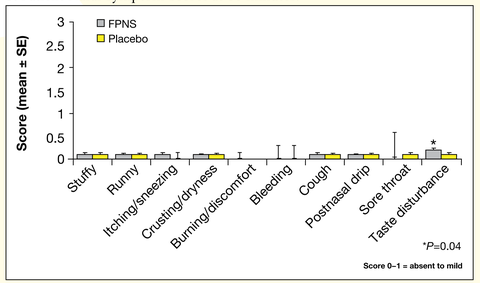
4. Episode patient acceptability assessments of overall treatment satisfaction.



Tolerability

- Treatment-related AEs were more frequent with FPNS compared with placebo and were mainly consistent with the pharmacologic effects of fentanyl.
- No significant nasal effects were reported in either the objective or subjective nasal assessments.
- **Figure 5** shows that on a 0–3 scale for 10 different adverse nasal symptoms, the average nasal symptom score was ≤0.2.

5. Patient Nasal Symptom Scores at 60 minutes.



CONCLUSIONS

- FPNS is rapidly efficacious for BTCP. Onset of analgesia (1-point reduction in PI) occurred in 33% of episodes by 5 minutes and 73% of episodes at 15 minutes; clinically meaningful PR (≥2-point reduction in PI) occurred in approximately 33% by 10 minutes and 66% by 30 minutes.
- The low use of rescue medication, good acceptability assessments and the high number of patients who elected to continue treatment post study support the ease of use and convenience of FPNS, and indicate that patients were satisfied with FPNS for treating their BTCP.
- FPNS provided rapid analgesia in BTCP and was safe and well tolerated by patients.

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