Efficacy and Safety of Fentanyl Pectin Nasal Spray Compared with Immediate-Release Morphine Sulfate Tablets in the Treatment of Breakthrough Cancer Pain: A Multicenter, Randomized, Controlled, Double-Blind, Double-Dummy Multiple-Crossover Study

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BACKGROUND: Immediate-release morphine sulfate (IRMS) remains the standard treatment for breakthrough cancer pain (BTCP), but its onset of effect does not match the rapid onset and short duration of most BTCP episodes.

OBJECTIVE: This study will evaluate the efficacy/tolerability of fentanyl pectin nasal spray (FPNS) compared with IRMS for BTCP.

METHODS: Patients (n = 110) experiencing one to four BTCP episodes/day while taking ≥60 mg/day oral morphine (or equivalent) for background cancer pain entered a double-blind, double-dummy (DB/DD), multiple-crossover study. Patients completing a titration phase (n = 84) continued to a DB/DD phase: 10 episodes of BTCP were randomly treated with FPNS and oral capsule placebo (five episodes) or IRMS and nasal spray placebo (5 episodes). The primary end point was pain intensity ($P < .05$ FPNS vs. IRMS) difference from baseline at 15 minutes (PID_{15}). Secondary end points were onset of pain intensity (PI) decrease (≥1-point) and time to clinically meaningful pain relief (CMPR, ≥2-point PI decrease). Safety and tolerability were evaluated by adverse events (AEs) and nasal assessments. By-patient and by-episode analyses were completed.

RESULTS: Compared with IRMS, FPNS significantly improved mean PID_{15} scores. 57.5% of FPNS-treated episodes significantly demonstrated onset of PI improvement by 5 minutes and 95.7% by 30 minutes. CMPR (≥2-point PI decrease) was seen in 52.4% of episodes by 10 minutes. Only 4.7% of patients withdrew from titration (2.4% in DB/DD phase) because of AEs; no significant nasal effects were reported.

CONCLUSION: FPNS was efficacious and well tolerated in the treatment of BTCP and provided faster onset of analgesia and attainment of CMPR than IRMS.

Breakthrough cancer pain (BTCP) is defined as "a transient exacerbation of pain that occurs either spontaneously, or in relation to a specific predictable or unpredictable trigger, despite relatively stable and adequately controlled background pain."[1] BTCP is a distinct entity, reported to affect up to 80% of all cancer patients with pain.[2] The typical BTCP episode is moderate to severe and sometimes even excruciating in intensity, rapid in onset (time from onset to peak pain intensity [PI] ~1–3 minutes),[3,4] and relatively short in duration (median 45 minutes).[4]

Currently, oral immediate-release morphine sulfate (IRMS) is the most common treatment for BTCP.[5,6] However, at least 30 minutes usually elapse before effectiveness is quantifiable,

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making IRMS too slow in onset for the management of BTCP.[7–9] Development of alternative BTCP treatments has focused on the opioid fentanyl because it has a relatively short half-life and its lipophilic nature is ideal for rapid transmucosal absorption. Oral transmucosal fentanyl formulations have been developed but have not fully met the need for very rapid onset of action. Furthermore, their use can be significantly limited by oral problems such as xerostomia, which is common (up to 78%) in patients with advanced cancer.[10–12]

Intranasal drug delivery offers a simple, acceptable route for strong analgesic administration; rapid, efficient drug absorption occurs because nasal tissues are highly vascularized and easily permeable and first-pass hepatic metabolism is avoided.[13,14] Conventional nasal fentanyl products are simple aqueous solutions delivered as sprays, but this may not be the most appropriate formulation because drug absorption can be variable and cannot be adequately controlled given the potential problems with nasal drip and with unpredictable drainage from the nose.[15] Recently, a fentanyl pectin nasal spray (FPNS) has been developed to optimize the absorption profile of fentanyl across the nasal mucosa. FPNS combines fentanyl with a proprietary delivery platform (PecSys®; Archimedes Pharma, Reading, UK), allowing fentanyl to be delivered as an aqueous solution in a low-volume fine mist of similarly sized droplets. When sprayed into the nasal passage, the pectin in the solution forms a thin layer of flexible gel on contact with calcium ions found in the nasal mucosa. This ensures no unwanted runoff or swallowing of the solution and rapid but controlled delivery of fentanyl.[15]

It has been reported[16] that FPNS provides significant pain relief when compared with placebo. A rapid clinical effect was observed in that study; superiority was demonstrated for onset of effect from 5 minutes after dosing and for clinically meaningful reduction in pain from 10 minutes after dosing. The main objective of this study was to evaluate the efficacy of FPNS compared with IRMS in the management of BTCP.

Methods

STUDY DESIGN

This multicenter, randomized, double-blind/double dummy (DB/DD), crossover study was conducted at 35 centers in Europe and India. The study was executed in accordance with all regulatory requirements and good clinical practice guidelines, approved by ethics committees and institutional review boards at the participating institutions, and conducted in accordance with the Declaration of Helsinki. Participating patients provided signed informed consent before enrollment.

The study consisted of four phases: screening (maximum 10 days), open-label dose-titration (maximum 14 days), DB/DD treatment (minimum 3 days, maximum 21 days), and end-of-treatment (1–14 days after last dose). The open-label dose-titration phase was used to identify an effective FPNS dose between 100 and 800 μg/episode of target BTCP. Patients had to complete the dose-titration phase (titration to an effective dose of FPNS that successfully treated 2 consecutive BTCP episodes without unacceptable adverse events [AEs]) to be eligible to continue to the DB/DD phase in which up to 10 BTCP episodes were treated (5 treated with FPNS and encapsulated oral placebo and 5 with IRMS and nasal spray placebo). The possible effective doses of FPNS were 100, 200, 400, and 800 μg administered using a multiuse nasal delivery device (Pfeiffer, Radolfzell, Germany). The 100- and 200-μg doses were administered using a 100-μg per 0.1-mL spray "low-dose" bottle and the 400- and 800-μg doses were administered using a 400-μg per 0.1-mL spray "high-dose" bottle. The multispray device featured a self-advancing countermechanism and emitted a loud click upon each actuation to confirm that a spray had been administered. Patients were instructed to take the oral treatment just before the nasal treatment for all episodes. The IRMS dose was determined according to the European Association for Palliative Care (EAPC) recommendations as one-sixth the total daily oral morphine dose equivalent of the patient's background opioid medication,[17] unless the patient had a previously identified effective dose of IRMS for BTCP.

PATIENTS

Participants were eligible if they had histologically confirmed diagnoses of cancer, were receiving fixed-schedule opioid regimens at a total dose equivalent to ≥60 mg/day oral morphine for background cancer-related pain, and had 1-4 episodes per day of BTCP. *BTCP* was defined as a transitory flare of moderate to severe pain that occurred on a background of persistent pain controlled to moderate intensity or less by the fixed-schedule opioid regimen. If a patient had more than one type of BTCP, then one was identified as the target BTCP.

Patients with uncontrolled or rapidly escalating background pain or who were medically unstable were ineligible for the study. Other exclusion criteria included breakthrough pain not related to cancer, past inability to tolerate fentanyl or other opioids, history of alcohol or substance abuse, treatment with monoamine oxidase inhibitors, anticipated therapy during study with any treatment that might affect pain levels (eg, radiotherapy, chemotherapy), treatment with another investigational drug within the previous 30 days, and any disorder or medication use likely to adversely affect normal functioning of the nasal mucosa.

EFFICACY ASSESSMENTS AND OUTCOME MEASURES

Electronic diaries (e-diaries, stored overnight on charger units that automatically connected to a central server for the daily upload of data) in local languages were used to collect patient data in real time during the dose-titration and DB phases. Patients were trained in their use at the investigator site and received written instructions in their local languages. Baseline PI before treatment of a BTCP episode was recorded on a standard 11-point numeric scale (0 = no pain, 10 = worst possible pain). After this measurement, the study drug was taken. The e-diary then provided cues so that PI and pain relief (PR) scores were recorded at 5, 10, 15, 30, 45, and 60

minutes after dosing. PR was measured on a 5-point numeric scale (0 = none, 4 = complete). Use of other rescue medications was also recorded in the e-diaries throughout the study.

SAFETY AND TOLERABILITY ASSESSMENTS

AEs were recorded throughout the study. All AEs reported within a 24-hour period of a dose of FPNS were associated with FPNS even though they might have been treated with IRMS subsequently during the DB period. Objective clinical nasal assessments were performed by the study physician at screening and at treatment end. Subjective nasal assessments were measured on a 4-point scale (0 = absent, 3 = severe) by the patient completing a 10-item questionnaire before the first use of the study drug, 1 hour after each dose of the study medication, and at the final study visit. Items rated were stuffy/blocked nose, runny nose, itching/sneezing, crusting/dryness, burning/discomfort, nosebleed, cough, postnasal drip, sore throat, and taste disturbance.

STATISTICAL ANALYSIS

The sample size was based on data from a similarly designed study of oral transmucosal fentanyl citrate compared with IRMS.[18] Based on the results of the previous study, it was estimated that the ratio of the effect size to SE for this study would be about 3.15 for a sample of 75 patients. Assuming 33% of patients would not complete the open-label dose-titration phase and an additional 33% would discontinue prior to taking 10 doses of the study drug, 180 patients were required to enter the open-label dose-titration phase to ensure that 80 patients completed the DB/DD treatment phase.

The primary end point was patient-averaged PI difference 15 minutes after dosing (PID_{15}). PID_{15} was defined as the difference between PI at baseline and at 15 minutes. Secondary end points included patient- and episode-averaged PID, summed PID (SPID), PI, PR, and summed PR (TOTPAR) scores at 5, 10, 15, 30, 45, and 60 minutes. Onset of analgesia with FPNS vs. IRMS was analyzed by assessing percentages of episodes with ≥1-point reductions in PI and PR scores at each time point. Onset of clinically meaningful pain relief (CMPR) was analyzed by assessing percentages of episodes with ≥2-point reductions or 33% reductions in PI and SPID.[19] PR scores were further examined, and the incidence of BTCP episodes with maximum PR as defined by a PR score of 4 on a 5-point scale (0–4) was determined over time. The percentage of BTCP episodes that required additional rescue medication within 60 minutes was also recorded.

Statistical analysis used a modified intent-to-treat (mITT) approach that included all patients in the randomized population who treated at least one pain episode with FPNS and oral placebo and at least one pain episode with IRMS and nasal spray placebo and, for each of these episodes, had at least one baseline and one postbaseline PI measurement. The safety analysis set included all patients who received at least one dose of FPNS or IRMS. Analyses were performed at the patient level (patient averages, percentages of patients) and at the episode level (percentages of episodes). The last observation carried forward was used to input missing data before average values were calculated for each patient. For the primary end point, analysis of covariance was used to compare treatments, with the PID_{15} score as the dependent variable and treatment group (FPNS and IRMS) and center as covariates. Secondary end points comparing treatment differences at each time point were analyzed using a model similar to the primary end point. Additionally, numbers and percentages of episodes in each treatment group achieving ≥1-point, ≥2-point, or ≥33% reductions in PI scores were summarized. All hypothesis testing was conducted using two-sided tests, with the alpha set at the 0.05 level.

Results

PATIENT DISPOSITION AND BASELINE DEMOGRAPHICS

A total of 135 patients were screened for the study, and 110 were enrolled in the titration phase (Fig. 1). Of these 110 patients, 106 took study medication and were included in the safety population. Mean age at baseline was 55.9 ± 12.3 years; 65.1% of patients were 60 or younger (Table 1). Among the 106 patients who commenced titration, opioids in use for background medication were morphine (59.4% of patients), fentanyl (33.0%), oxycodone (8.5%), buprenorphine (1.9%), pentazocine (1.9%), and hydromorphone (1.9%) (Table 1). A total of 93.4% of patients were using a single opioid for background pain; the most common of these was morphine (49.1%). The mean daily background oral morphine equivalent was 201.9 mg.

Eighty-four patients (76%) identified an effective and tolerable FPNS dose during the titration phase (Fig. 1). The mean ± SD dose of IRMS was 29.4 ± 38.9 mg. Of the 84 patients in the DB/DD treatment phase, 79 (94.0%) completed the study and were included in the mITT population. A total of 740 BTCP episodes—372 treated with FPNS, 368 treated with IRMS—were considered mITT-evaluable.

EFFICACY

Analysis of the primary end point, patient-averaged PID_{15}, revealed a significant difference between BTCP episodes treated with FPNS and those treated with IRMS; mean ± SE was 3.02 ± 0.21 for FPNS doses and 2.69 ± 0.18 for IRMS ($P < .05$) (Fig. 2A). Statistical superiority of FPNS compared with IRMS on patient-averaged PID scores was maintained at each point from 15 minutes through 60 minutes ($P < .05$) (Fig. 2B).

Mean baseline PI scores were slightly higher for patient-averaged FPNS-treated episodes than for IRMS-treated episodes (7.76 vs. 7.65, respectively; $P < .05$). After treatment, mean PI scores were lower for FPNS-treated episodes than for IRMS-treated episodes from 10 minutes onward, with statistical significance between treatments shown at all points from 30 to 60 minutes ($P \leq .05$). Patient-averaged PR scores were greater after FPNS administration than after IRMS administration at all observed time points, with statistical significance

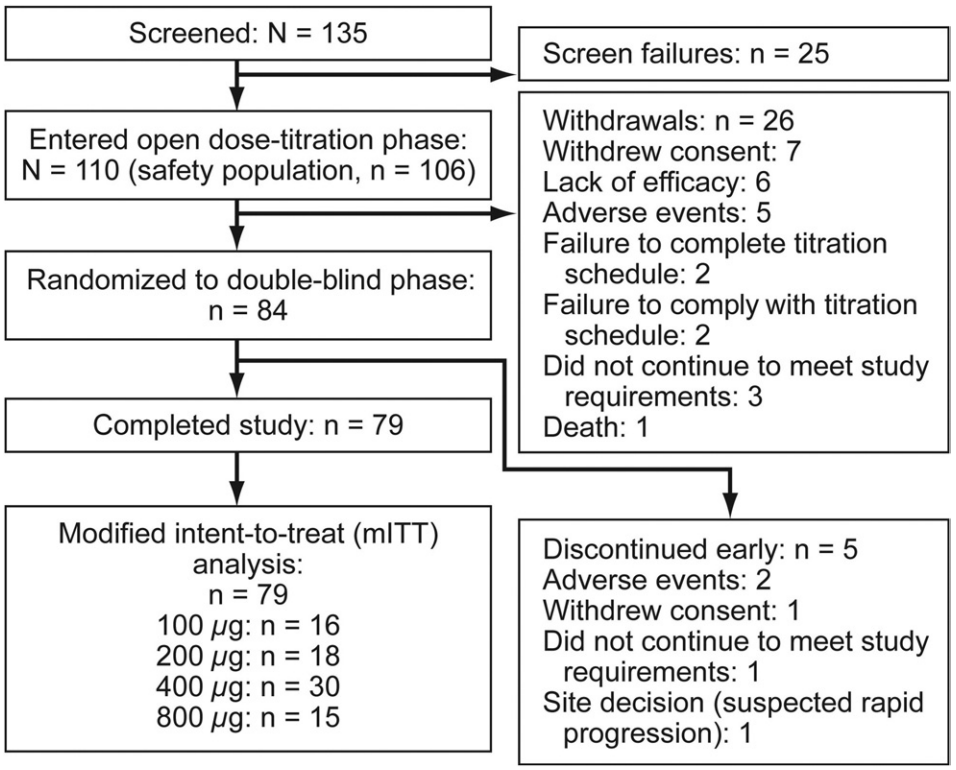

Figure 1 Study Disposition (CONSORT Diagram)

shown at all points from 30 to 60 minutes ($P \leq .005$). Similarly, patient-averaged mean differences in TOTPAR were significant from 15 minutes and at all points to 60 minutes ($P < .05$).

Episode-level analyses were performed as indicators of the consistency of effect, and percentages of episodes with PR scores ≥1 or ≥1-point reductions in PI score were calculated to evaluate the onset of effect. The superiority of FPNS vs. IRMS was apparent as early as 5 minutes after dosing, with significant differences in the percentages of episodes showing a ≥1-point change in PI and PR scores after FPNS treatment vs. IRMS treatment ($P < .05$ and $P < .001$, respectively). Statistical significance between treatments was maintained for episodes with PR scores ≥1 point at 5, 10, and 30 minutes ($P < .05$) but was not statistically significant at 15 minutes ($P = .0508$). Results for episodes showing ≥1-point reductions in PI showed some temporal variation ($P < .05$ at 30 minutes, $P > .05$ at other time points). Similarly, significantly more episodes with CMPR (mean PI score reductions ≥2 or ≥33%) were observed after the administration of FPNS than that of IRMS at 10 and 15 minutes after dose (both $P < .05$) (Fig. 3). There was no significant difference between treatments from 30 minutes. In addition, significantly more episodes had a ≥2-point mean reductions in SPID score at 10 minutes after FPNS than after IRMS administration ($P < .05$). The superiority of FPNS over IRMS in providing CMPR at 10 minutes was further supported by significantly higher percentages of episodes with mean reductions in SPID score of ≥2, ≥3, and ≥4. Similarly, the number of treated episodes with a ≥33% reduction in PI score at 10 minutes was significantly larger after FPNS use than after IRMS use (33.9% vs. 28.3%, $P < .0357$) and at 15 minutes (55.4% vs. 47.3%, $P < .0056$).

The number of BTCP episodes achieving a maximum PR score of 4 with FPNS was higher compared with IRMS at 30 minutes (17.6% vs. 12.6%, $P = .05$) and significantly higher at 45 (31.1% vs. 21.5%, $P < .01$) and 60 (50.1% vs. 34.3%, $P < .0001$) minutes (Fig. 4). Approximately half the BTCP episodes at 60 minutes had achieved maximum pain relief with FPNS compared with just over one-third for IRMS. This represented a 46.1% improvement in maximal pain relief efficacy with FPNS.

Slightly lower proportions of FPNS-treated (3.0%) than IRMS-treated (3.8%) episodes necessitated the use of rescue medication from 0 to 60 minutes after treatment, but the difference did not reach statistical significance ($P = .57$).

SAFETY

Overall, more treatment-emergent AEs (TEAEs) were reported after FPNS than after IRMS treatment, and a higher percentage of TEAEs was observed after 400- and 800-μg doses of FPNS than after 100- and 200-μg doses. TEAEs with FPNS were mainly mild to moderate in severity. The most commonly reported TEAEs following last treatment with FPNS were vomiting, somnolence, dehydration, and nausea (Table 2). Only 4.7% of patients withdrew from titration because of AEs.

Table 1

Summary of Patient Demographic Characteristics (Safety Population)

PARAMETER	SUMMARY STATISTICS
n	106
Age (years)	
Mean ± SE	55.9 ± 1.19
Range	18–82
≤60	65.1
>60	34.9
Race, n (%)	
Caucasian	52 (49.1)
Black	1 (0.9)
Indian	53 (50.0)
Sex, n (%)	
Male	57 (53.8)
Female	49 (46.2)
Weight (kg)	
Mean ± SE	59.8 ± 1.81
Range	30.0–129.4
Eastern Cooperative Oncology Group score (%)	
0	4.7
1	59.4
2	35.8
Baseline opioid use,[a] n (%)	
Morphine	63 (59.4)
Fentanyl	35 (33.0)
Oxycodone	9 (8.5)
Pentazocine	2 (1.9)
Buprenorphine	2 (1.9)
Hydromorphone	2 (1.9)

[a] Some subjects used more than one opioid medication.

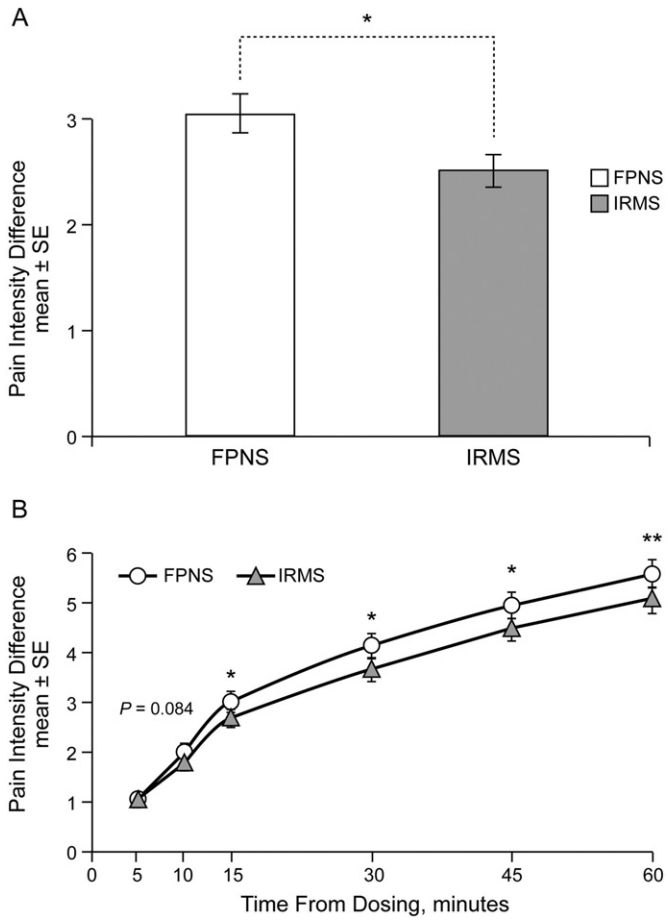

Figure 2 PID Scores at 15 Minutes (A) and At All Time Points (Patient-Averaged Values) (B)

(A) *$P < .05$ FPNS vs. IRMS. (B) *$P < .05$ FPNS vs. IRMS, **$P < .01$ FPNS vs. IRMS

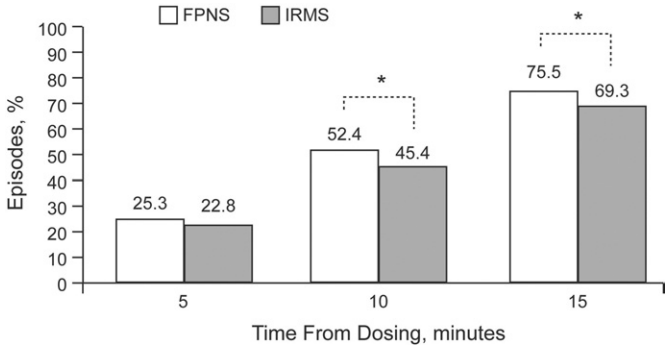

Figure 3 Percentages of Episodes with Clinically Meaningful Pain Relief (≥2-Point Reductions in Pain Intensity)

*$P < .05$ FPNS vs. IRMS

Fourteen serious AEs (12 events after FPNS treatment of the preceding episode, two events after IRMS treatment of the preceding episode) were reported by 8 patients (6 after FPNS, 2 after IRMS). A total of 6 deaths occurred during the study: 3 patients died during screening before taking any study drug, 2 died during the dose-titration phase, and 1 died during the DB/DD phase. Most serious AEs and deaths were considered not related to the study drug; however, 1 death was assessed as possibly related to the study drug (circulatory insufficiency, hypotension, anuria following last treatment with FPNS). No treatment-emergent changes in mean values of laboratory or clinical safety parameters occurred that were suggestive of safety issues associated with either treatment. No patients were suspected of abuse or diversion of the study drug at any center involved in the trial.

NASAL TOLERABILITY

There were no changes on objective clinical assessment of the nose. At the final study visit, ≤5.7% of patients reported itching/sneezing, crusting/drying of the nose, stuffy/blocked nose, cough, sore throat, burning/discomfort, nasal bleeding, or postnasal drip above a mild intensity (ie, intensity >1). One patient experienced severe taste disturbance at the final study visit. The overall percentage of patients reporting any of

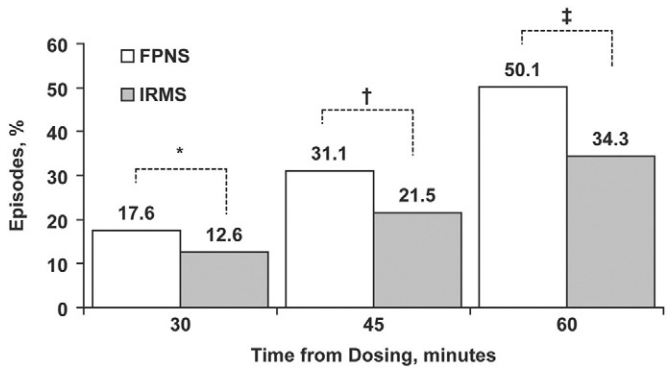

Figure 4 Percentages of Episodes with Maximal Pain Relief (PR = 4)

*P = .05, †P < .01, ‡P < .0001 FPNS vs. IRMS

these events at mild or moderate intensity before the first use of the study drug (≤10.7%) decreased at the final study visit (≤7.3%). No statistically significant difference was noted between FPNS and IRMS (nasal placebo) treatments for any subjective nasal tolerability parameter.

Discussion

This is the first study to compare the efficacy and tolerability of intranasal fentanyl with IRMS in the management of BTCP. It demonstrated a statistically significant improvement in PID_{15} of FPNS compared with IRMS ($P < .05$). Significant benefits in episode PR scores and PID scores were reported with FPNS compared to IRMS within only 5 minutes of dosing, and clinically meaningful levels of pain relief were observed across several parameters from 10 minutes after dosing.

The efficacy of FPNS within 5 minutes of dosing was also reported in an earlier study in which the onset of CMPR was again observed within 10 minutes of administration.[16] This rapid onset of effect is of major importance in the management of BTCP. Although IRMS remains a common therapy for BTCP, it is often criticized for its 30-minute onset of effect, which is usually not fast enough to meet patients' needs.[7] The clinical relevance of this delayed onset of effect was clearly observed in our study. Using a commonly accepted metric of ≥2-point reduction in PI as an indicator of clinically meaningful response,[19] significantly more episodes met the criterion for meaningful pain relief with FPNS than with IRMS at 10 and 15 minutes ($P < .05$). The cumulative advantage of FPNS at 10 minutes was further supported by statistically significant differences in the percentages of episodes showing SPID values at the ≥2-point, ≥3-point, and ≥4-point thresholds ($P = .0146$, $P = .0348$, $P = .0338$, respectively).

From 30 minutes, the differences between the two treatments remained the same or started to close, suggesting that IRMS started to match the analgesic effect of FPNS only from this time. It is, of course, likely that a proportion of BTCP episodes resolved spontaneously by 30 minutes. However, a further examination of BTCP episodes achieving a maximum PR score of 4 showed that FPNS was more effective at providing maximal pain relief for the full duration of a typical BTCP episode, which surveys have shown lasts an average of 45–60 minutes (range 5–360 minutes).[4] This correlates with the pharmacokinetics of FPNS, which studies have shown still provides therapeutic levels of plasma fentanyl at 60 minutes.[20] At 60 minutes, approximately half the episodes had achieved maximum pain relief compared with just over one-third for IRMS, representing a 46.1% improvement in maximal pain relief efficacy with FPNS.

Efficacy scores for IRMS at the early time points were not entirely consistent with the expected pharmacodynamic profile of oral morphine[7,9] and were higher than those demonstrated by previous studies in BTCP (e.g., PID_{60} of IRMS was ~5 points in the present study vs. ~3.5 points in the study by Coluzzi et al.[18]). Although this may suggest that some BTCP episodes were short-lived, the multiple-crossover design means that this was likely equally true for both treatments. Another potential explanation is a significant effect of the trial design. A "training effect" of patient expectations (similar to a placebo response) possibly occurred during the open-label dose-titration phase with FPNS. Thus, having experienced an effective dose of FPNS, it is possible that patients were primed to expect rapid pain relief. In support of this notion, recent brain imaging studies have suggested that the main effect of placebo arises from the reduction of anticipation of pain during placebo conditioning (or, in the present study, the titration phase).[21,22] Given that the perception of pain is highly subjective, this training effect might have impacted the results, especially at earlier time points. Studies of BTCP characteristics have focused primarily on duration from onset until peak pain.[23]

More TEAEs were reported after FPNS than after IRMS treatment. However, it is difficult to relate the occurrence of AEs to a specific treatment in a study using a short-interval, multiple-crossover design. In studies of medications for BTCP, this problem is further compounded because all patients are given a background treatment of daily opioid therapy, which is expected to contribute to the overall AE rate. In this study, all AEs reported within a 24-hour period of an FPNS dose were conservatively associated with FPNS, even if the patient had also been treated that day with IRMS. This led to obvious skewing toward a higher AE rate with FPNS. Safety results include the open-label dose-titration phase; therefore, each patient treated had significantly more episodes with FPNS than with IRMS, again skewing the comparison. Two deaths occurred after FPNS administration in the open-label dose-titration phase and one occurred after IRMS administration in the DB/DD treatment phase. All were likely related to the underlying disease process. All TEAEs that led to study drug discontinuation were recognized side effects of fentanyl or other opioids or related to the underlying disease process.

The study design was comparable to that of previous studies of other fentanyl formulations for BTCP.[18] This crossover

Table 2

Summary of Common Treatment-Emergent Adverse Events (Safety Population)

	FPNS				
PREFERRED TERM	100 μg (N = 105)	200 μg (N = 82)	400 μg (N = 60)	800 μg (N = 23)	IRMS TOTAL (N = 80)
Overall	25 (23.8%)	15 (18.3%)	20 (33.3%)	8 (34.8%)	13 (16.3%)
Vomiting	4 (3.8%)	2 (2.4%)	3 (5.0%)	2 (8.7%)	3 (3.8%)
Somnolence	2 (1.9%)	4 (4.9%)	3 (5.0%)	0 (0.0%)	1 (1.3%)
Dehydration	1 (1.0%)	3 (3.7%)	1 (1.7%)	1 (4.3%)	1 (1.3%)
Nausea	1 (1.0%)	1 (1.2%)	2 (3.3%)	2 (8.7%)	1 (1.3%)
Constipation	2 (1.9%)	1 (1.2%)	3 (5.0%)	0 (0.0%)	1 (1.3%)
Dizziness	2 (1.9%)	2 (2.4%)	2 (3.3%)	0 (0.0%)	0 (0.0%)
Headache	1 (1.0%)	2 (2.4%)	1 (1.7%)	0 (0.0%)	0 (0.0%)
Asthenia	1 (1.0%)	1 (1.2%)	1 (1.7%)	0 (0.0%)	1 (1.3%)

FPNS = fentanyl pectin nasal spray; IRMS = immediate-release morphine sulfate.

design is considered most suitable for studies of BTCP because each patient acts as his or her own control, thereby eliminating the significant issues of between-patient variability in reporting pain and in BTCP characteristics. As discussed, however, this does complicate efforts to identify and interpret the relationship between medication and TEAEs. Another strength of the study is the use of a double-dummy as an additional measure against bias or placebo effect because all patients were given either placebo or active drug by both delivery routes for each episode during the double-blind assessment. Limitations of the study include its relatively short duration and the lack of titration to an effective dose of IRMS. However, longer-term studies with FPNS have been conducted,[24] and the dose of IRMS was calculated using the equivalent 4-hour dose of morphine, per EAPC guideline recommendations at the time the study was conducted.[17] Although it could be argued that this approach is not ideal, even in routine practice, it was the intention of the study to reflect the clinical use of IRMS as much as possible. Moreover, the higher than expected efficacy scores for IRMS appear to rule out any underdosing. Although the use of an open-label dose-titration phase to identify a tolerable but effective dose (enrichment approach) can draw criticism[25,26] and might have led to a training effect, the fact that rapid-onset opioids for the treatment of BTCP must always be titrated means this approach mirrors clinical practice. Furthermore, only 5.5% of patients failed to identify an effective dose because of lack of efficacy, indicating that this approach and the dose range selected are appropriate to clinical practice.

Conclusions

The results of this study demonstrate that FPNS is efficacious, safe, and well tolerated for the treatment of breakthrough pain in a population of cancer patients receiving around-the-clock opioid treatment for chronic cancer-related pain. Treatment with FPNS was effective at delivering significant early, clinically meaningful reductions in pain that matched or exceeded the therapeutic effect of IRMS as well as providing more complete pain relief throughout the duration of the BTCP episodes treated.

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Conflicts of interest Disclosure: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr. Davies has served as a consultant for Archimedes and received support from Archimedes to travel to meetings to present trial data. No other conflicts of interest were reported.

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