Consistency of Efficacy, Patient Acceptability, and Nasal Tolerability of Fentanyl Pectin Nasal Spray Compared with Immediate-Release Morphine Sulfate in Breakthrough Cancer Pain

Andrew Davies, MBBS, MSc, MD, FRCP, Thomas Sitte, Frank Elsner, MD, Carlo Reale, MD, Jose Espinosa, MD, David Brooks, MD, and Marie Fallon, MB, ChB, MD, FRCP
The Royal Marsden NHS Foundation Trust (A.D.), Sutton, United Kingdom; PalliativNetz Osthessen (T.S.), Fulda; RWTH Aachen University (F.E.), Aachen, Germany; Sapienza University of Rome (C.R.), Rome, Italy; Institut Català d’Oncologia (J.E.), Barcelona, Spain; Chesterfield and North Derbyshire Royal Hospital NHS Trust (D.B.), Chesterfield; and Edinburgh Cancer Research Centre (M.F.), University of Edinburgh, Edinburgh, United Kingdom

Abstract

Context. We recently reported that fentanyl pectin nasal spray (FPNS) provides superior pain relief from breakthrough cancer pain (BTCP) compared with immediate-release morphine sulfate (IRMS), with significant effects by five minutes and clinically meaningful pain relief from 10 minutes postdose.

Objectives. To report the consistency of efficacy, tolerability, and patient acceptability of FPNS vs. IRMS.

Methods. Patients (n = 110) experiencing one to four BTCP episodes/day while taking ≥60 mg/day oral morphine (or equivalent) for background pain entered a double-blind, double-dummy (DB/DD), multiple-crossover study. Those who completed an open-label titration phase (n = 84) continued to a DB/DD phase; 10 episodes were randomly treated with FPNS and overencapsulated placebo or IRMS and nasal spray placebo (five episodes each). Pain intensity (PI) and pain relief scores were assessed. Patient acceptability scores were assessed at 30 and 60 minutes. Safety and tolerability were assessed by adverse events (AEs) and nasal assessments.

Results. Per-episode analysis revealed that FPNS consistently provided relief from pain more rapidly than IRMS; by 10 minutes, there were significant differences in PI difference scores and in the percentages of episodes showing clinically meaningful pain relief (P < 0.05). Overall acceptability scores were significantly greater for FPNS than for IRMS at 30 (P < 0.01) and 60 (P < 0.05) minutes. Patients were “satisfied/very satisfied” with the convenience (79.8%)
and ease of use (77.2%) of FPNS. Only 4.7% of patients withdrew from titration because of AEs; no significant nasal effects were reported.

**Conclusion.** This study demonstrates that FPNS is efficacious, well accepted, and well tolerated by patients with BTCP. J Pain Symptom Manage 2011;41:358–366. © 2011 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

**Key Words**
Fentanyl, intranasal, breakthrough pain, cancer, pain management, patient acceptability

---

**Introduction**

Pain is one of the most devastating symptoms of cancer. About one-third of people with cancer have pain at diagnosis, which increases to more than two-thirds of people with advanced disease. Breakthrough cancer pain (BTCP), 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,” has been reported to affect up to 80% of all cancer patients with pain. Although individual BTCP episodes can vary in duration and intensity, the typical BTCP episode is rapid in onset (average one to three minutes) and relatively short in duration (median duration 30 minutes). Most patients report their BTCP as severe to excruciating in intensity, and studies report a median number of 1.5 to six BTCP episodes per day. When it occurs, BTCP is associated with distress, functional impairment, poor quality of life, and increased health care costs. Moreover, its occurrence has a direct impact on patient satisfaction with pain control and opioid therapy.

At present, oral immediate-release morphine sulfate (IRMS) is the most common treatment for BTCP. However, the peak effect of IRMS is achieved in an average of 60 minutes, potentially leaving patients in severe pain. This mismatch between need for rapid relief and late onset of effect of oral opioid formulations for BTCP has led to considerable effort toward alternative treatments to manage BTCP.

To meet the broad needs of the patient with BTCP, the development of new treatments should take into account consistency of efficacy (i.e., reliability of pain relief response), patient tolerability, and acceptability. Indeed, the tolerability and acceptability of a product can often be limiting factors in the treatment of patients with BTCP. For example, a significant proportion of patients with advanced cancer have oral problems such as xerostomia, which can make oral transmucosal administration of opioids difficult or uncomfortable. Such factors are especially important because poor adherence to pain medication regimens has been identified as a major barrier to effective pain control.

Intranasal drug delivery offers a simple and acceptable route for the rapid administration of strong analgesics. Recently, a fentanyl pectin nasal spray (FPNS) was developed to optimize the absorption profile of fentanyl across the nasal mucosa. Randomized controlled studies have demonstrated that FPNS provides superior pain relief compared with placebo and IRMS. These studies have demonstrated that significant effects on pain could be recorded after only five minutes after a dose and that clinically meaningful reductions in pain intensity could be seen from 10 minutes after a dose. We report here further details from the second study of the consistency of efficacy (per-episode secondary efficacy analyses and rescue medication use), tolerability, and patient acceptability of FPNS vs. IRMS.

**Methods**

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.

**Study Design**

The study consisted of four phases: a screening phase (maximum 10 days), an open dose-titration phase (maximum 14 days), a DB/DD treatment phase (minimum three days; maximum 21 days), and an end-of-treatment phase (one to 14 days after the last dose). The open 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 two 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 (five treated with FPNS and encapsulated oral placebo, five with IRMS and nasal spray placebo). For all episodes, patients were instructed to take the oral treatment just before the nasal treatment. IRMS dose was determined for each patient as one-sixth the total daily oral morphine dose equivalent of the patient’s background opioid medication32 or the patient’s previously identified “effective” dose of IRMS for BTCP.

**Patients**

Patients were eligible to participate if they had a histologically confirmed diagnosis of cancer, were receiving a fixed-schedule opioid regimen at a total daily dose equivalent to or greater than 60 mg/day oral morphine for background cancer-related pain, and had one to four episodes per day of moderate-to-severe BTCP. Patients who had uncontrolled or rapidly escalating background pain or whose conditions were medically unstable were ineligible for the study. Other exclusion criteria included past inability to tolerate fentanyl or other opioids and any disorder or medication use likely to adversely affect normal functioning of the nasal mucosa.

**Efficacy and Acceptability Assessments and Outcome Measures**

Electronic diaries were used to collect patient data in real time during the dose-titration and double-blind phases. Baseline PI before treatment of a BTCP episode was recorded on an 11-point numeric scale (0 = no pain; 10 = worst possible pain). After this baseline measurement, the study drug was taken. The e-diary then provided signals so that PI and pain relief scores were recorded at 5, 10, 15, 30, 45, and 60 minutes after dosing. Pain relief was measured on a 5-point numeric scale (0 = none; 4 = complete). Use of rescue medications also was recorded in the e-diaries throughout the study.

After treatment of each BTCP episode in the double-blind phase, patients were asked to rate overall satisfaction (30 and 60 minutes), satisfaction with speed of relief (30 and 60 minutes), and reliability (60 minutes only) of the nasal spray using a 4-point scale (1 = not satisfied; 4 = very satisfied). In addition, at the end of the study (after the last treated BTCP episode), patients rated the ease of use and convenience of the nasal spray.

**Safety and Tolerability Assessments**

AEs were recorded throughout the study. Objective nasal assessments were performed by the study clinician at screening and study end to assess nasal obstruction (assessed on a 4-point scale: 0 = absent; 1 = mild mucosal thickening; 2 = moderate edema, narrowing of airways; and 3 = severe obstruction), inflammation (assessed on 4-point scale: 0 = absent; 1 = mild crusting or blood staining; 2 = moderate crusting, fresh blood, pus, or cyanotic mucosa; and 3 = severe septal perforation or mucosal ulceration), presence of discharge, and color of mucosa. Subjective nasal assessments were performed by the patient using a 10-item questionnaire (each item rated on a 4-point scale: 0 = absent; 1 = mild crusting or blood staining; 2 = moderate crusting, fresh blood, pus, or cyanotic mucosa; and 3 = severe) before the first use of study drug, 60 minutes after each dose of study medication, and at the final study visit. The items rated were stuffy-blocked nose, runny nose, itching/sneezing, crusting/dryness of nose, burning/discomfort of nose, bleeding of nose, cough, postnasal drip, sore throat, and taste disturbance.

**Statistical Analysis**

The modified intent-to-treat (mITT) analysis set included all patients in the randomized population who had treated at least one pain episode with each study medication (FPNS or IRMS) and had, for those episodes, a baseline
and at least one subsequent PI measurement. Efficacy analyses at the episode level for the mITT population included all mITT-evaluable episodes for mITT patients only. The safety analysis set included all patients who received at least one dose of FPNS. The primary endpoint was the patient-averaged PI difference 15 minutes after dosing (PID15) and is reported elsewhere.31

Episode-level analyses were performed as indicators of the consistency of effect, and outcome measures included episode analyses of PI, PI difference from baseline (PID), summed PID (SPID), pain relief, and total pain relief (TOTPAR). In addition, the percentage of episodes showing clinically meaningful pain relief (defined as a two-point or greater reduction in PI) was analyzed. For the acceptability assessments, responses were averaged across episodes to derive the average score for each question for a patient. This was then used to derive the average patient score for each question for each treatment group. For ease-of-use and convenience assessments performed after the last treated episode, patient-averaged scores by treatment were categorized as “dissatisfied/neither satisfied nor dissatisfied” (score <3) and “satisfied/very satisfied” (score ≥3).

AE data during the DB/DD phase were summarized by treatment. Nasal tolerability was assessed by recording the percentage of patients exhibiting mild, moderate, or severe symptoms and by the percentages of nasal problems resulting in study withdrawal. All statistical tests were performed at the $P \leq 0.05$ level (two-sided).

### Results

#### Patient Disposition and Baseline Characteristics

The mean age at baseline was $55.9 \pm 12.3$ years (median age 57.0 years); 63.1% of patients were aged 60 years or older.

Of the 110 patients enrolled in the open dose-titration phase, 106 patients took study medication and were included in the safety population. Overall, 84 (79.2%) patients identified an effective and tolerable FPNS dose during the titration phase and were randomly assigned to double-blind treatment. Of the patients who withdrew from the titration phase, six (5.5%) patients withdrew because of lack of efficacy, and five (4.5%) patients withdrew because of AEs. Of the 84 patients randomly assigned, 79 (94%) completed the study. For the mITT population, 372 BTCP episodes were treated with FPNS and 368 episodes were treated with IRMS.

#### Per-Episode Efficacy Analyses

Per-episode analysis revealed that FPNS consistently provided relief from pain more rapidly than IRMS; by 10 minutes, there were statistically significant differences in PID scores ($P < 0.05$) and in the percentages of episodes showing clinically meaningful pain relief (Table 1). The cumulative superiority of FPNS vs. IRMS at the 10-minute time point was further supported by statistically significant differences in the percentages of episodes showing SPID values at the $\geq 2$, $\geq 3$, and $\geq 4$-point thresholds ($P = 0.0146$, $P = 0.0348$, $P = 0.0338$, respectively). By 15 minutes, significantly more episodes achieved maximum TOTPAR

| Table 1: Efficacy Analysis of Clinically Meaningful Pain Relief by Episode |
|--------------------|-------|-------|-------|-------|-------|-------|
| Episode, %         | 5 Minutes | 10 Minutes | 15 Minutes | 30 Minutes | 45 Minutes | 60 Minutes |
| ≥2-point reduction in PI |
| FPNS               | 25.3   | 52.4   | 75.5   | 86.8   | 89.2   | 91.4   |
| IRMS               | 22.8   | 45.4   | 69.3   | 82.9   | 88.6   | 89.4   |
| $P$ value          | NS     | <0.05  | <0.05  | NS     | NS     | NS     |
| Pain relief score ≥2 |
| FPNS               | 20.2   | 39.4   | 60.2   | 82.4   | 87.4   | 91.3   |
| IRMS               | 20.1   | 34.8   | 53.4   | 71.4   | 83.4   | 87.4   |
| $P$ value          | NS     | NS     | <0.05  | <0.001 | NS     | NS     |
| Maximum TOTPAR ≥33% |
| FPNS               | —      | 38.0   | 52.3   | 59.8   | 76.2   | 83.4   |
| IRMS               | —      | 32.6   | 43.3   | 51.0   | 64.3   | 74.9   |
| $P$ value          | NS     | ≥0.01  | ≤0.01  | <0.001 | <0.01  | <0.01  |

NS = not significant.
of \( \geq 33\% \) (showing cumulative benefit accruing at that time point) after FPNS compared with IRMS \((P \leq 0.01)\). Significant differences in TOTPAR scores between the two groups were maintained until 60 minutes (Table 1). From the 30-minute time point onward, the differences between the two treatments either remained the same or started to close, suggesting that IRMS was starting to have a comparable therapeutic effect from 30 minutes.

Overall, the percentage of episodes requiring rescue medication was similar between the two groups; 97.0% of episodes of BTCP treated with FPNS and 96.2% of episodes treated with IRMS did not require additional rescue medication within 60 minutes \((P = 0.57)\).

Patient Acceptability

Mean patient acceptability scores are summarized in Table 2. The overall mean patient-averaged acceptability assessment score \(\text{"How satisfied are you overall with the nasal spray you have used to treat this episode of BTCP?"} \) was significantly greater for FPNS than for IRMS at 30 and 60 minutes after dose \((P \leq 0.01 \text{ for both})\). Similarly, the mean assessment scores for the speed of relief (30 and 60 minutes) and the episode reliability (60 minutes) of the nasal spray also favored FPNS over IRMS, with statistically significant differences evident at both time points \((P \leq 0.01)\).

Overall acceptability assessments after the last treated episode demonstrated that 61 (77.2%) patients reported overall acceptability assessment scores \(\geq 3\) (satisfied to very satisfied) for the ease of use of FPNS. Similarly, 65 (79.8%) patients reported overall acceptability assessment scores \(\geq 3\) for convenience (Fig. 1). At the end of the study, 70% of patients elected to continue treatment with FPNS in an open-label extension protocol.

Patient Tolerability

Treatment-emergent AEs (TEAEs) have been presented elsewhere (Fallon, manuscript submitted). In brief, slightly more TEAEs were reported after FPNS than after IRMS, and most TEAEs with FPNS were mainly mild to moderate in severity. Overall, only eight patients (six after treatment with FPNS and two after treatment with IRMS) experienced TEAEs that resulted in the discontinuation of study drug.

Nasal Tolerability

Objective Examination. No significant nasal effects were reported using clinician nasal assessments (Table 3). Mild nasal obstruction was experienced by six (5.7%) patients at screening, which decreased to two (2.2%) patients at study end. No patient had nasal inflammation at screening or at study end. One (0.9%) patient had severe nasal discharge, and one (0.9%) patient had pale mucosa at screening; however, at study end, no patients exhibited these problems.

Subjective Nasal Tolerability. There were no consistent patterns of reporting of nasal symptoms such as stuffy/blocking nose, runny nose, itching/sneezing, crusting/dryness of nose, burning/discomfort, nasal bleeding, cough, postnasal drip, sore throat, or taste disturbance. No patient reported any of these nasal tolerability parameters at an intensity of \( > 2 \) to 3 (moderate or severe). No statistically significant difference was noted between FPNS and IRMS treatments (Fig. 2).

<table>
<thead>
<tr>
<th>Question</th>
<th>Time Point (Minutes)</th>
<th>FPNS ((n = 79))</th>
<th>IRMS ((n = 78))</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;How satisfied are you overall with the nasal spray you have used to treat this episode of BTCP?&quot; (\text{ (Scale 1–4)})</td>
<td>30</td>
<td>2.91 (0.059)</td>
<td>2.64 (0.065)</td>
<td>(\leq 0.01)</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>3.01 (0.057)</td>
<td>2.73 (0.064)</td>
<td>(\leq 0.01)</td>
</tr>
<tr>
<td>&quot;How satisfied are you with the speed of relief you gained with the nasal spray in the treatment of this episode of BTCP?&quot; (\text{ (Scale 1–4)})</td>
<td>30</td>
<td>2.92 (0.061)</td>
<td>2.62 (0.068)</td>
<td>(\leq 0.01)</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>3.01 (0.062)</td>
<td>2.72 (0.065)</td>
<td>(\leq 0.01)</td>
</tr>
<tr>
<td>&quot;How satisfied are you with the reliability of the nasal spray you have used to treat this episode of BTCP?&quot; (\text{ (Scale 1–4)})</td>
<td>60</td>
<td>3.03 (0.057)</td>
<td>2.74 (0.065)</td>
<td>(\leq 0.01)</td>
</tr>
</tbody>
</table>

Values are mean \((\pm SE)\).
Discussion

The results of this study provide complementary data to the primary efficacy and safety analyses (Fallon, manuscript submitted) and demonstrate consistency of efficacy for FPNS. Moreover, FPNS was well tolerated nasally and was well accepted by patients experiencing BTCP. Strengths of the study include the crossover study design (each patient acted as his or her own control) and use of a DB/DD design as an additional measure against bias. Limitations of the study include its relatively

Fig. 1. Overall patient acceptability assessments (ease of use and convenience) of a nasal spray after last treated episode ($n=79$). Missing values: 12.7%.

Discussion

The results of this study provide complementary data to the primary efficacy and safety analyses (Fallon, manuscript submitted) and demonstrate consistency of efficacy for FPNS. Moreover, FPNS was well tolerated nasally and was well accepted by patients experiencing BTCP. Strengths of the study include the crossover study design (each patient acted as his or her own control) and use of a DB/DD design as an additional measure against bias. Limitations of the study include its relatively

Table 3

<table>
<thead>
<tr>
<th>Objective Nasal Tolerability Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Parameter</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Obstruction</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Inflammation</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Discharge present</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Color mucosa</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
short duration and the lack of titration of IRMS. However, when this study was executed, the current recommendation from the European Association for Palliative Care guidelines was to use one-sixth of the around-the-clock dose of oral morphine as an effective rescue medication dose for BTCP. Furthermore, although the use of an open-label dose-titration phase to identify a tolerable but effective dose can be criticized, the fact that rapid-onset opioids for the treatment of BTCP must always be titrated means that this approach mirrors routine practice.

In current clinical practice, many patients with cancer are treated as outpatients, and, as such, treatment strategies rely on patient and/or caregiver adherence to the prescribed regimens. Studies have shown that patients are particularly inconsistent in taking as-needed analgesics in the prescribed manner and, as a result, receive suboptimal treatment of their pain. All medications for BTCP should, therefore, be efficacious, well tolerated, acceptable, and easy to use. The design of this study included episode analyses of pain relief as a secondary efficacy measure because such analyses provide a good measure of how consistent the efficacy is across episodes. The results show that FPNS consistently provides clinically meaningful pain relief faster than IRMS. The low use of additional rescue medication with FPNS (3%) also lends support to the consistency of efficacy.

Therapeutic efficacy was reached significantly earlier in the course of the BTCP episodes treated with FPNS than in those treated with IRMS. As reported in the primary efficacy analyses, significantly more episodes achieved a greater than one-point reduction in PI at the five-minute time point when treated with FPNS than when treated with IRMS, and this early benefit also was seen in the FPNS vs. placebo study. By 10 minutes, there were also significant differences in PID scores and in the percentages of episodes showing clinically meaningful pain relief. From 30 minutes, the differences in standard efficacy outcome measures between the two treatments remained the same or started to close, suggesting that IRMS started to match the analgesic effect of FPNS from this time. Interestingly, the patient-reported acceptability assessments that were made at the 30- and 60-minute time points favored FPNS over IRMS at both.

When questioned about the acceptability of different routes of administration of analgesia for BTCP, patients in one survey of cancer patients referred to a specialist palliative care unit indicated that they feared it would be difficult to administer the drug through the nasal
route or that the drug would catch in the throat or taste bad and that they were unfamiliar with the idea of using the nasal route. In that survey, the conventional oral route was considered the most acceptable but was associated with a slow onset of analgesia. The nasal tolerability results of this study are, therefore, reassuring given that FPNS caused no significant nasal findings on objective examination and minimal symptoms on subjective reporting (including taste). No patient withdrew from the study because of nasal tolerability problems.

Most patients rated FPNS convenient and easy to use, indicating that once a patient tries the nasal route, they find it highly acceptable. It is noteworthy that more than 70% of patients from this study continued into a 16-week open-label study. Patients and caregivers may find the nasal route more convenient and acceptable than other routes of administration, such as rectal suppository or subcutaneous injection. Indeed, ease of access to the nose means that caregivers can quickly and safely administer FPNS even when a patient is unable to do so. In addition, the device and accompanying storage container may contribute to the convenience of FPNS administration. They are easy for patients to keep with them at all times. When a dose is administered, an audible click can be heard with each spray, and a dose counter that is provided allows visualization of the remaining number of sprays. A child-resistant storage container is provided with FPNS to make it more difficult for accidental exposure to occur when children are present.

In summary, we have previously reported that FPNS provides rapid and effective analgesia with a time course more suitable than that of IRMS for treating the typical BTCP episode. The consistency of efficacy, excellent tolerability, and patient acceptability data reported in the present analyses further demonstrate its suitability for the management of BTCP.

**Disclosures and Acknowledgments**

There was no financial support provided for this study. The authors disclose the following: Andrew Davies: consultant/advisor for Archimedes and honoraria from Archimedes; Thomas Sitte: consultant for Archimedes, Nycomed, Haupt Pharma, and instructor/speaker for Janssen-Cilag, Mundipharma, Pfizer, ProStrakan, Grüenthal; Frank Elsner: advisory board member/speaker for Archimedes, Cephalon, Nycomed, ProStrakan, Meda, Janssen-Cilag, Mundipharma, Grüenthal; Carlo Reale: no grant or financial support to declare; Jose Espinosa: no grant or financial support to declare; David Brooks: advisory board member for Archimedes, and advisory board member/speaker for Cephalon, Nycomed; Marie Fallon: research fellow support from Archimedes.

The authors wish to acknowledge i3Research, which conducted the study, and the technical and editorial support provided by Anita Chadha-Patel at ApotheCom.

**References**

10. Hwang SS, Chang VT, Kasimis B. Cancer breakthrough pain characteristics and responses to