IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: S. George Kottayil et al.	)	SUBLINGUAL FENTANYL SPRAY
Serial No.: 11/698,739	)	Examiner: Wegert, Sandra
Filed: January 25, 2007	)	Group Art Unit: 1646
Atty. Dkt. No.: INS10763P00090US	)	Confirmation No. 4756

DECLARATION OF DR. LARRY DILLAHA TO 37 CFR 1.132

Commissioner For Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Madam:

Your Declarant, Dr. Larry Dillaha, hereby declares and states as follows:

1. I am currently employed by Insys Therapeutics, Inc. ("Insys"), the Assignee of the present application, as Chief Medical Officer. My duties include overseeing clinical development, regulatory affairs, medical affairs and the formulation scientists at Insys. I have been continuously employed by Insys since April 2010.

2. I have over 10 years of experience in the field of pharmaceutical formulation development with experience in working on both solid dose and liquid formulation development. I have overseen the formulation development of numerous products. Additionally, I have worked closely with the U.S. Food and Drug Administration ("FDA") on clinical development of such products. I have been involved with the filing for drug approval of numerous drugs before the FDA over my career.

3. I have reviewed the present application, U.S. Pat. Appl. No. 11/698,739, as well as the last Office Action dated June 8, 2012.

4. Fentanyl is a potent, short acting narcotic analgesic used, *inter alia*, for the treatment of breakthrough pain in late-stage cancer patients. Such patients are typically treated for pain with a baseline dosage of a long acting pain medication. However, for episodes of breakthrough pain, a fast-acting, highly potent pain reliever (e.g., fentanyl) is desirable. Accordingly, effective treatment for pain in 5 minutes compared to 10 or 15 minutes or longer is significant.

5. SUBSYS® is the registered trademark for the Insys brand of sublingual fentanyl spray. SUBSYS® is exemplified and claimed in the above-noted patent application. The specific SUBSYS® formulations are as described in Exhibit A.

6. These SUBSYS® formulations were evaluated in Phase III, randomized, double-blind, placebo-controlled, multicenter studies to evaluate the safety and efficacy.

7. Patients having breakthrough cancer pain began to experience statistically significant pain relief as early as 5 minutes after dosing. This is consistent with notion that the claimed dose needs to have a meaningful blood concentration at about 5 minutes. See SUBSYS® package insert (Figure 1 in Section 12.3) (Exhibit 1) and the Final Study Report (See efficiency results and conclusion) (Exhibit 2).

8. No marketed, competitive fentanyl product has been able to show statistically significant pain relief any earlier than 10 minutes. See Exhibit B and Exhibits 3-7.

9. These publications, Exhibits 1-7 described above, demonstrate that the presently claimed unit dose provides effective pain relief at significantly faster times than placebo or competitive fentanyl products.

10. Accordingly, the presently claimed unit dose provides efficacious pain relief at significantly faster times relative to other transmucosal immediate release fentanyl formulations, which is both unexpected and, more importantly, a distinct clinical benefit.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed: Larry Dillaha Dated: 17 Sept 2012

EXHIBIT A

Compositions of Fentanyl Sublingual Spray – 100, 200, 400, 600, and 800 µg Dose

Component	Function	Quantity per 100 µL				
		1 mg/mL (100 µg dose)	2 mg/mL (200 µg dose)	4 mg/mL (400 µg dose)	6 mg/mL (600 µg dose)	8 mg/mL (800 µg dose)
Fentanyl base	Active Ingredient	100 µg	200 µg	400 µg	600 µg	800 µg
Dehydrated alcohol	Cosolvent	49.6 mg	49.6 mg	49.6 mg	49.6 mg	49.6 mg
Propylene glycol	Cosolvent	4.5 mg	4.5 mg	4.5 mg	4.5 mg	4.5 mg
L-Menthol	Flavor	45.0 µg	45.0 µg	45.0 µg	45.0 µg	45.0 µg
Xylitol	Sweetener	2.7 mg	2.7 mg	2.7 mg	2.7 mg	2.7 mg
Purified water	Solvent	33.2 mg	33.1 mg	32.9 mg	32.7 mg	32.5 mg

EXHIBIT B

Product	Company	1st Positive Efficacy Timepoint (minutes)	Title of Article	Exhibit #
SUBSYS®	Insys	5	A Randomized, Double-Blind, Placebo-Controlled Multi-Center Study to Evaluate the Safety and Efficacy of Fentanyl Sublingual Spray (Fentanyl SL Spray) for the Treatment of Breakthrough Cancer Pain	2
ACTIQ®	Teva/Cephalon	15 (Figure 1)	Oral transmucosal fentanyl citrate (OTFC) for the treatment of breakthrough pain in cancer patients; a controlled dose titration study	3
FENTORA®	Cephalon	15 (Figures 2 and p. 810, 2nd full paragraph)	A Randomized, Placebo-controlled Study of Fentanyl Buccal Tablet for Breakthrough Pain in Opioid-treated Patients with Cancer	4
ONSOLIS®	Meda	15 (Figures 2 and 3)	Fentanyl buccal soluble film (FBSF) for breakthrough pain in patients with cancer: a randomized, double-blind, placebo-controlled study	5
ABSTRAL®	ProStrakan	10 (p. 528, 2nd full paragraph)	Long-term effectiveness and tolerability of sublingual fentanyl orally disintegrating tablet for the treatment of breakthrough cancer pain	6
LAZANDA®	Archimedes	10 (p. 620, Efficacy section)	A multicenter, placebo-controlled, double-blind, multiple-crossover studyof FEntanyl Pectin Nasal Spray (FPNS) in the treatment of breakthrough cancer pain	7

EXHIBIT 2

1. TITLE PAGE

FINAL STUDY REPORT

TITLE	A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study to Evaluate the Safety and Efficacy of Fentanyl Sublingual Spray (Fentanyl SL Spray) for the Treatment of Breakthrough Cancer Pain.
STUDY DESIGN (PHASE)	III
PROTOCOL NUMBER	INS-05-001
DRUG PRODUCT	Fentanyl sublingual spray (Fentanyl SL Spray) Active ingredient: Fentanyl base Unit strengths: 100, 200, 400, 600, and 800 µg fentanyl per actuation (unit dose spray device) Administered dose strengths: 100, 200, 400, 600, 800, 1200 (2x600), and 1600 (2x800) µg fentanyl
DRUG SUBSTANCE	Fentanyl base
INDICATION	Breakthrough cancer pain
SPONSOR	Insys Therapeutics, Inc. 10220 S. 51st Street, Suite 2 Phoenix AZ 85044
PRINCIPAL INVESTIGATOR	A list of the investigators involved in this study, along with clinical site information, is included in Appendix 16.1.4.
MEDICAL MONITOR	Mauricio Calero, MD Clinimetrics Research Inc.
STUDY DATES	Initiation (First subject enrolled) 18 October 2007 Completion (Database lock) 22 February 2010
REPORT DATE	03 December 2010 (Version 3.0)

This study was conducted under Good Clinical Practice according to the Declaration of Helsinki (2004).

2. SYNOPSIS

Name of Sponsor	Insys Therapeutics, Inc.
Name of Product	Fentanyl sublingual spray (Fentanyl SL Spray)
Name of Active Ingredient	Active ingredient: Fentanyl base Unit strengths: 100, 200, 400, 600, and 800 µg fentanyl per actuation (unit dose spray device) Administered dose strengths: 100, 200, 400, 600, 800, 1200 (2x600), and 1600 (2x800) µg fentanyl
Indication (phase)	Breakthrough cancer pain (Phase III)
Title of Study	A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study to Evaluate the Safety and Efficacy of Fentanyl Sublingual Spray (Fentanyl SL Spray) for the Treatment of Breakthrough Cancer Pain.
Publications	None to date
REPORT PARTICULARS	
Report date	03 December 2010 (Version 3.0)
Period of study	18 October 2007 (first subject enrolled) to 22 February 2010 (database lock)
Principal Investigator	A list of the investigators involved in this study, along with clinical site information, is included in Appendix 16.1.4.
OBJECTIVES	
Primary Objective	Assess the efficacy of Fentanyl SL Spray for the treatment of breakthrough cancer pain in opioid-tolerant subjects.
Secondary Objectives	Evaluate the safety of Fentanyl SL Spray in these opioid-tolerant subjects. An additional objective was to assess treatment satisfaction with medication.
METHODOLOGY	
Study Design	This was a Phase III randomized, double-blind, placebo-controlled multi-center study of the clinical response to Fentanyl SL Spray as a treatment for breakthrough cancer pain. Subjects were to be evaluated at Screening Visit for the use and response to opioids in the previous 24 hours. The Screening Visit was to occur 28 +7 days prior to the Open-label Titration Visit. Approximately 130 subjects who experienced one to four breakthrough cancer pain episodes each day and who were receiving a stable dose of scheduled 24-hour opioids to manage baseline pain were to be entered into a titration period for a maximum of 21 (+5) days to establish the optimal dose of Fentanyl SL Spray required to effectively treat their breakthrough cancer pain. Subjects who established an optimal dose of Fentanyl SL Spray were to be entered into the randomized, double-blind, placebo-controlled period of the study (double-blind period) for a maximum of 21 + 5 days to determine the efficacy

	of the selected Fentanyl SL Spray dose compared to placebo treatment in management of breakthrough cancer pain. In the double-blind period, subjects were to treat 10 episodes of breakthrough cancer pain using 10 blinded study medication doses consisting of seven Fentanyl SL Spray and three placebo doses placed in random order. Subjects were to complete the pain assessments (Pain Intensity and Pain Relief) from baseline until 60 minutes after dosing and a subject's Global Evaluation of Study Medication at 30 minutes and 60 minutes after each dose of study medication. Subjects were to return for a Final Visit 21 +5 days after beginning the double-blind period or within 7 days of completing 10 double-blind treatments, whichever occurred first. Any subject withdrawn from the study was to return for an Early Termination Visit. Safety was assessed throughout the double-blind period by monitoring laboratory changes, vital signs, physical examination changes and adverse events. An additional 30-day safety Follow-up Period was to occur after the final visit.
Treatments	In the titration period, subjects were to begin at the 100 µg dose of Fentanyl SL Spray and then titrate upward until there was sufficient pain relief with tolerable side effects established for treating two consecutive episodes of breakthrough cancer pain at the same dose level. Fentanyl SL Spray dose strengths of 100, 200, 400, 600, 800, 1200 (2x600), and 1600 (2x800) µg were available in the titration period for the subject to establish a dose of Fentanyl SL Spray that effectively treated breakthrough cancer pain. The dose of Fentanyl SL Spray that successfully treated breakthrough pain was then to be used in the double-blind period. Subjects were to complete 10 double-blind treatments within the 21 +5 day double-blind period. Fentanyl was administered as a sublingual spray.
Treatment Duration	The planned treatment duration may have been up to 52 days (titration period and double-blind period). Subjects may have been enrolled in the study for up to 122 days, as follows: Screening Visit to Open-label Titration Visit - 35 days (28 +7) Titration Period - 26 days (21 +5) Double-blind Period - 26 days (21 +5) Final Visit to Follow-up Telephone Contact - 35 days (30 +5).
Study Drug	Fentanyl sublingual spray (Fentanyl SL Spray). The reference treatment was a placebo administered as a sublingual spray. Fentanyl SL Spray dose strengths of 100, 200, 400, 600, 800, 1200 (2x600), and 1600 (2x800) µg were provided for the titration and double-blind periods.
Batch Numbers	The overall batch number for the clinical packaging for all efficacy supply was 7013611. The batch numbers for the Fentanyl SL Spray used in this study were: 707164 (100 µg), 706049 (200 µg), 706050 (400 µg), 706051 (600 µg), 706052 (800 µg), 706051 (1200 µg, dosed as 2x600 µg), 706052 and 709677 (1600 µg, dosed as 2x800 µg). The batch number for the placebo spray used in this study was 706046.
SUBJECT POPULATION	
Number Planned	Approximately 130 opioid-tolerant subjects were to be enrolled in the titration period of the study. It was expected that at least 92 of these subjects would proceed to the double-blind period.
Major Inclusion Criteria	Subject were to have a documented clinical diagnosis of cancer with a controlled level of background pain requiring a stable dose of scheduled baseline opioid treatment of at least 60 mg/day of morphine, 25 µg/hr of transdermal fentanyl, or an equianalgesic dose of another opioid. The medication for relief of breakthrough pain was to be equivalent to ≥5 mg immediate-release morphine or its equivalent as a short-acting opioid (e.g.

	oxycodone, hydrocodone, or codeine with acetaminophen). The subject was to have a stable daily pattern averaging one to 4 breakthrough pain episodes during the 4 day Screening Period.
Major Exclusion Criteria	• Current use of commercially available oral short-acting fentanyl for breakthrough pain. Subjects previously on Actiq® or Fentora® can be enrolled if they have had a seven day washout. • Rapidly increasing/uncontrolled pain. • Painful erythema, oedema or ulcers under the tongue.
ASSESSMENTS	
Efficacy	Efficacy assessments performed at 5, 10, 15, 30, 45 and 60 minutes after each dose of study medication included Pain Intensity (PI) and Pain Relief (PR). The Subject's Global Evaluation of Study Medication was to be made at 30 and 60 minutes after each dose of study medication. The primary efficacy endpoint of the study was the Summed Pain Intensity Differences (SPID) at 30 minutes after dosing ($SPID_{30}$). The secondary efficacy endpoints were Total Pain Relief (TOTPAR) at 30 minutes ($TOTPAR_{30}$) after dosing and Subject's Global Evaluation of Study Medication, recorded at 30 minutes after dosing. The measurements of TOTPAR and SPID were calculated over the 60 minutes treatment period for each of the 10 doses of study medication used to treat breakthrough pain in the double-blind period. A Treatment Satisfaction Questionnaire for Medication (TSQM) was completed by subjects to record their satisfaction with the treatment medication.
Safety	Adverse events (AE) were recorded and reported for safety assessment. The effects of treatment on vital signs and clinical laboratory measurements were assessed throughout the study. Safety was assessed on the following criteria: • AEs/Serious Adverse Events (SAEs) occurring throughout the study • Laboratory evaluations (serum chemistry, hematology, urinalysis) • Vital signs assessments (blood pressure, heart rate, respiration rate and temperature) • Physical examinations

STATISTICAL METHODS AND ANALYSIS	
Efficacy	Analyses of efficacy were based on the intent-to-treat population defined as all randomized subjects who provided informed consent, took study medication and had at least one pain measurement following administration of study medication. The analysis of the primary endpoint, $SPID_{30}$, was preceded by a data reduction algorithm. Within each subject, $SPID_{30}$ was summarized over breakthrough pain episodes treated with Fentanyl SL Spray and over episodes treated with placebo. The difference within subject of the two $SPID_{30}$ summaries was then calculated. Additionally, within each subject the mean baseline pain intensity was calculated over all breakthrough pain episodes treated with study medication (regardless of treatment). Within-subject differences in $SPID_{30}$ were then analyzed using analysis of co-variance (ANCOVA) using the within-subject mean baseline pain intensity as a covariate. The secondary endpoints of $TOTPAR_{30}$ and Subject Global Evaluation of Study Medication, recorded at 30 minutes post-dose, were analyzed in a similar manner. The overall type 1 error rate for the primary and secondary analyses was set at 0.05. The *p*-values from the secondary endpoints were adjusted for multiple comparisons using the

	Hochberg method; however, neither endpoint was to be considered significant unless the primary endpoint was determined to be significant. As a sensitivity analysis, the within-subject summaries of treatment effect were analyzed using the Wilcoxon signed rank test. As additional sensitivity analyses, the measurements of PI, Pain Intensity Difference (PID), and SPID were analyzed using a single mixed model in which PI was the dependent variable. Inference on PID and SPID at all time points, including the 30 minute primary end point, was performed within this model, as these measures are linear combinations of PI at various time points. The fixed effects of the model were treatment, time, and treatment-time interaction. The random effects were subject and breakthrough pain episode within subject, and the random error associated with time period within episode.
Safety	Safety analyses (adverse events, labs, and vital signs) were performed on the safety population, defined as all randomized subjects who took at least one dose of study drug. Descriptive statistics were presented for demographics, baseline characteristics, summary of laboratory parameters, vital signs and physical examinations.
STUDY POPULATION RESULTS	
Demographics	**Titration population:** mean age was 55.6 ± 12.2 years (range from 24 to 85 years), with 77% of subjects <65 years of age and 95% of subjects <75 years of age. 53% of subjects were female and 91% of subjects were White. **ITT population:** mean age was 54.1 ± 11.7 years (range from 24 to 85 years, with 83% of subjects <65 years of age and 97% of subjects <75 years of age. 54% of subjects were female and 91% of subjects were White.
Subject Disposition	A total of 130 subjects were treated during the titration period of the study, and comprised the safety population. Of these, 98 subjects (75%) were randomized to the double-blind period of the study. A total of 35 subjects (27%) in the safety population withdrew from the study early, with the most common reasons for termination being voluntary withdrawal (16 subjects or 12%) and AEs (7 subjects or 5%). Considering only those subjects randomized to the double-blind period of the study, 3 subjects (3%) terminated the study early (one subject withdrew due to each of an AE, non-compliance and voluntary withdrawal). There were 95 subjects (73% of the safety population) who completed the double-blind period, and 90 subjects (69%) rolled over to the safety portion of the study. There were 79 subjects (61%) who completed 10 doses of study drug according to the protocol.
EFFICACY RESULTS	
	The primary efficacy endpoint for this study was the evaluation of $SPID_{30}$. Higher SPID values indicate improvements in pain intensity. $SPID_{30}$ was significantly improved ($p<0.0001$) when breakthrough pain episodes were treated with Fentanyl SL Spray compared to placebo. Mean (± SD) $SPID_{30}$ scores were 640.3 ± 458.8 for Fentanyl SL Spray and 399.6 ± 391.2 for placebo, with a difference of 240.7 ± 362.9 between the two treatments. SPID values at all time points were significantly improved when pain was treated with Fentanyl SL Spray compared with placebo. The proportion of subjects with improved SPID values when treated with Fentanyl SL Spray ranged from 60% at $SPID_5$ to 79% at $SPID_{30}$. One of two secondary efficacy endpoints for this study was the evaluation of $TOTPAR_{30}$. Higher TOTPAR values indicate an improvement in total pain relief. For $TOTPAR_{30}$, TOTPAR was significantly improved ($p<0.0001$) when breakthrough pain episodes were treated with Fentanyl SL Spray compared to placebo. Mean (± SD) $TOTPAR_{30}$ scores were 78.3 ± 20.4 for Fentanyl SL Spray and 61.0 ± 20.8 for placebo, with a difference of 17.3 ± 19.5 between the two treatments. The p-value for $TOTPAR_{30}$ was adjusted for multiplicity using Hochberg's method. The adjusted p-value remained significant

	($p<0.0001$). The proportion of subjects with improved TOTPAR values when treated with Fentanyl SL Spray ranged from 60% at $TOTPAR_5$ to 84% at $TOTPAR_{60}$. Subject Global Evaluation of Study Medication at 30 minutes was the second secondary efficacy endpoint. Higher subject global evaluation values indicate an improvement in how a subject perceives the effectiveness of the study medication. At 30 minutes post-dose, the subject global evaluation was significantly improved ($p<0.0001$) when breakthrough pain episodes were treated with Fentanyl SL Spray compared to placebo. Mean (± SD) subject global evaluation scores at 30 minutes were 2.8 ± 0.8 for Fentanyl SL Spray and 2.0 ± 0.8 for placebo, with a difference of 0.8 ± 0.9 between the two treatments. The p-value for subject global evaluation scores at 30 minutes was adjusted for multiplicity using Hochberg's method. The adjusted p-value remained significant ($p<0.0001$). Additional efficacy endpoints included TOTPAR at time points other than 30 minutes post-dose and global evaluation at 60 minutes. TOTPAR values at all time points were significantly improved when pain was treated with Fentanyl SL Spray compared with placebo. Subject global evaluation scores at 60 minutes were also significantly improved ($p<0.0001$) when pain was treated with Fentanyl SL Spray compared with placebo. Improvements in pain assessments, measured by pain intensity, pain intensity difference and pain relief, were observed as early as 5 minutes for Fentanyl SL Spray on each measure, and were durable through to 60 minutes. The use of rescue medication within 60 minutes of treatment was significantly lower when pain was treated with Fentanyl SL Spray than with placebo ($p<0.0001$). Rescue medication was required for 10% of episodes treated with Fentanyl SL Spray and for 28% of episodes treated with placebo. Conversely, 90% of breakthrough pain episodes treated with Fentanyl SL Spray did not require the use of rescue medication. Within each episode, the time to rescue medication usage was compared between treatments using a Cox Proportional Hazards model, accounting for the clustering of multiple episodes with subject. The hazard ratio of 0.33 (95% CI 0.24, 0.45) indicates there was approximately a 67% reduction in the likelihood of using rescue pain medication during treatment of breakthrough cancer pain with Fentanyl SL Spray compared with placebo. This finding was statistically significant ($p<0.0001$). The TSQM was completed at the beginning of the titration period (baseline) and at the end of the titration period (Visit 1 of the double-blind period). The TSQM domain scores for Effectiveness, Side Effects, Convenience, and Overall Satisfaction range from 0 to 100, with higher scores indicating greater treatment satisfaction. For each domain, scores were higher at the end of the titration period as compared to the beginning of the period. The greatest difference was seen in the Effectiveness domain. Improvements at the end of the titration period were also observed for each of the individual TSQM questions. At the end of the period, 89% of subjects were satisfied, very satisfied or extremely satisfied with this medication, compared with 41% of subjects at baseline. Similarly, 90% of subjects at the end of the period were at least satisfied with the amount of time it took the medication to start working, compared with 21% of subjects at baseline. Comparable increases in satisfaction were also seen for the other questions, including symptom relief, confidence in the medication, and convenience of use. There were significant $SPID_{30}$ subject-specific treatment differences (all p-values ≤ 0.0017) for the age (<65 and ≥65 years), gender, type of around-the-clock pain medication used, type of prior breakthrough pain medication used and successful dose of Fentanyl SL Spray subgroups.
SAFETY RESULTS	
All Adverse Events	The safety population consisted of 130 subjects. At least 1 AE was reported for 78 subjects (60%) in the titration period and for 47 subjects (48%) in the double-blind

	period. During the titration period, the most frequently-reported system organ class (SOC) was gastrointestinal disorders, for which AEs were reported for 36 subjects (28%). The most frequently-reported AE was nausea, which was reported for 17 subjects (13%). Other frequently-reported AEs included somnolence (11 subjects or 9%), dizziness and vomiting (each reported by 10 subjects or 8%) and pyrexia (8 subjects or 6%). Severe AEs were experienced by 10 subjects (8%) in the titration period. Most subjects experienced events assessed as at least possibly related to study drug (51 subjects or 39%). By category, 33 subjects (25%) experienced AEs that were probably related to study drug, and 18 subjects (14%) experienced AEs that were possibly related. During the double-blind period, the most frequently-reported SOC was gastrointestinal disorders, for which 17 subjects (17%) reported an AE. The most frequently-reported AE was nausea, which was reported in 7 subjects or 7%. Other frequently-reported AEs included hyperhidrosis and oedema peripheral (each reported in 5 subjects or 5%), and vomiting (4 subjects or 4%). Severe AEs were experienced by 5 subjects (5%) in the double-blind period. Most subjects experienced events assessed as not related to study drug (38 subjects or 39%). By category, 2 subjects (2%) experienced AEs that were probably related to study drug, and 7 subjects (7%) experienced AEs that were possibly related. A composite summary of AEs associated with study drug use or mode of administration was tabulated. There were 33 subjects (25%) and 6 subjects (6%) in the titration and double-blind periods, respectively, who experienced an AE related to study drug use. Most of these AEs occurred in the higher dose groups (≥ 600 µg fentanyl). There were 5 subjects (4%) in the titration period who experienced an AE related to study drug mode of administration; no subjects in the double-blind group experienced any of these AEs.
Deaths and Other Serious Adverse Events	Three deaths were recorded in this study, each of which was assessed as unrelated to study drug. In each case, the subject's death was related to the progression of the underlying disease of cancer. A similar frequency of SAEs was observed during both periods, with 7 subjects (5%) and 6 subjects (6%) reporting SAEs in the titration and double-blind periods, respectively. In the titration period, 5 subjects (4%) experienced severe SAEs and 2 subjects (2%) experienced moderate SAEs. In the double-bind period, 3 subjects (3%) experienced each of moderate and severe SAEs. All SAEs were assessed as not related to study drug.

CONCLUSIONS

Episodes of breakthrough pain are common in patients with chronic pain due to cancer. Breakthrough cancer pain is generally characterized by a rapid onset and a short duration (up to two hours). Given that patients may experience several of these episodes on a daily basis, an effective treatment with a rapid onset of action would form a significant component of the overall pain management regimen. Fentanyl is a narcotic analgesic used to relieve pain. Fentanyl SL Spray is formulated to deliver fentanyl to the oral mucosa of cancer patients, offering a convenient method of delivery for patients who might otherwise have difficulty in administering oral medications.

In this study, subjects treated episodes of breakthrough cancer pain either with Fentanyl SL Spray or a placebo spray. Various pain assessments, including pain intensity and pain relief, were performed at time points from 5 to 60 minutes post administration of study drug. Patients taking Fentanyl SL Spray to treat breakthrough cancer pain began to experience statistically significant pain relief as early as 5 minutes following dosing. The significant effect of Fentanyl SL Spray was durable through 60 minutes, the last evaluation time point.

Fentanyl SL Spray significantly reduced breakthrough cancer pain based on the primary efficacy endpoint of $SPID_{30}$, and at every other SPID time point. These results were consistent with those obtained for other pain evaluations, including total pain relief and a subject global evaluation. At each time point for each pain assessment, the effect of Fentanyl SL Spray at relieving breakthrough cancer pain was significantly greater than that of the placebo spray.

Satisfaction with the use of Fentanyl SL Spray was assessed with the TSQM, administered at the beginning and the end of the titration period. For every TSQM domain, scores were higher at the end of the titration period as

compared to the beginning of the period, indicating an improvement in satisfaction with the pain relief medication. At the end of the period, 89% of subjects were at least satisfied with Fentanyl SL Spray, compared with 41% of subjects who were satisfied with their current pain medication at baseline. Similarly, 90% of subjects at the end of the period were at least satisfied with the amount of time it took Fentanyl SL Spray to start working, compared with 21% of subjects at baseline. Comparable increases in satisfaction were also seen for the other questions, including symptom relief, confidence in the medication, and convenience of use.

There were no new safety issues identified for Fentanyl SL Spray. Three deaths were recorded in this study, each of which was assessed as unrelated to study drug. In each case, the subject's death was related to the progression of the underlying disease of cancer. The rate of serious adverse events was low, with approximately 5% of subjects experiencing an SAE in each of the titration and double-blind periods. The most frequently reported AE was nausea. AEs assessed with an intensity of severe and which were at least possibly related to study drug were experienced by 3 subjects; none of these events was considered serious.

EXHIBIT 3

PAIN

Pain 79 (1999) 303–312

Oral transmucosal fentanyl citrate (OTFC) for the treatment of breakthrough pain in cancer patients: a controlled dose titration study

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Abstract

Oral transmucosal fentanyl citrate (OTFC) is a novel opioid formulation in which the potent synthetic μ-agonist fentanyl is embedded in a sweetened matrix that is dissolved in the mouth. It is undergoing investigation as a treatment for cancer-related breakthrough pain, a prevalent phenomenon defined as a transitory flare of moderate to severe pain that interrupts otherwise controlled persistent pain. There have been no controlled trials of other treatments for this condition. To evaluate the safety and efficacy of ascending doses of OTFC, a novel controlled dose titration methodology was developed that applied blinding and randomization procedures to the evaluation of recurrent pains in the home environment. The study was a multicenter, randomized, double-blind dose titration study in ambulatory cancer patients. The sample comprised adult patients receiving a scheduled oral opioid regimen equivalent to 60–1000 mg oral morphine per day, who were experiencing at least one episode per day of breakthrough pain and had achieved at least partial relief of this pain by use of an oral opioid rescue dose. After collection of 2 days of baseline data concerning the efficacy of the usual rescue drug, patients were randomly treated with either 200 or 400 μg OTFC unit doses in double-blind fashion. Up to two breakthrough pains each day could be treated with up to four OTFC unit doses per pain. OTFC in unit doses containing 200, 400, 600, 800, 1200 or 1600 μg of fentanyl citrate were available for the study. The unit dose was titrated upward in steps until the patient had 2 consecutive days on which breakthrough pain could be treated with the single unit dose, titration was ineffective at a 1600 μg unit dose, or 20 days elapsed. To maintain the double-blind, orders to titrate up were ignored one-third of the time according to a pre-defined randomization schedule accessible only to an unblinded study pharmacist. Main outcome measures included, numeric or categorical measures of pain intensity, pain relief, and global assessment of drug performance. Dose response relationships were found suggesting that the methodology was sensitive to opioid effects. Seventy-four percent of patients were successfully titrated. There was no relationship between the total daily dose of the fixed schedule opioid regimen and the dose of OTFC required to manage the breakthrough pain. Although the study was not designed to provide a definitive comparison between OTFC and the usual rescue drug, exploratory analyses found that OTFC provided significantly greater analgesic effect at 15, 30 and 60 min, and a more rapid onset of effect, than the usual rescue drug. Adverse effects of the OTFC were typically opioid-related, specifically somnolence, nausea and dizziness. Very few adverse events were severe or serious. This study demonstrated the feasibility of controlled trial methodology in studies of breakthrough pain. OTFC appears to be a safe and effective therapy for breakthrough pain, and dose titration can usually identify a unit dose capable of providing adequate analgesia. If the lack of a relationship between the effective OTFC dose and fixed schedule opioid regimen is confirmed, dose titration may be needed in the clinical use of this formulation. Further investigation of OTFC as a specific treatment for breakthrough pain is warranted.

Keywords: Oral transmucosal fentanyl citrate; Pain; Cancer

1. Introduction

Pain related to medical illnesses, such as cancer, typically fluctuates, and patients often report the experience of transient flares. When these transient flares of pain are clinically significant and interrupt a background pain that is otherwise

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controlled and tolerated, they are commonly described as 'breakthrough pains.' Breakthrough pains that are precipitated by a voluntary action, such as movement, are often labeled 'incident' pains. In the cancer setting, breakthrough or incident pain usually implies a moderate to severe transitory pain that punctuates a persistent background pain that is generally well controlled by opioid therapy.

Breakthrough pain is a challenging clinical phenomenon. The prevalence of breakthrough pain in a prospective survey of inpatients with cancer pain was 64% (Portenoy and Hagen, 1990) and surveys indicate that the likelihood of a satisfactory response to opioid therapy is lower among those who report this type of pain than those who do not (Mercadante et al., 1992; Bruera et al., 1995). Clinicians commonly observe a strong association between physical and psychosocial impairments, and either the frequency or intensity of these transient pains.

The potential for adverse consequences associated with breakthrough pain has been the impetus for the development of specific therapeutic strategies. In those populations treated with long-term opioid therapy, the most common approach is the co-administration of a supplemental short-acting analgesic 'as needed,' along with the scheduled long-acting opioid regimen. Guidelines for cancer pain management now include instructions for the use of such a supplemental opioid analgesic (World Health Organization, 1990; American Pain Society, 1992; Jacox et al., 1994), and the term 'rescue dose' is widely applied to describe this approach. Based on clinical observations, the selection of rescue drugs typically focuses on pure μ-opioid agonists with relatively short half-lives and time-action profiles, characterized by a rapid onset, early peak effect and a duration long enough to treat most breakthrough pains. In the cancer population, morphine sulfate, oxycodone and hydromorphone are commonly used for this purpose.

Oral transmucosal fentanyl citrate (OTFC) is currently undergoing investigation as a new treatment for breakthrough pain. In this formulation, the potent synthetic opioid, fentanyl, is incorporated into a sweetened matrix that is dissolved in the mouth, allowing rapid absorption of part of the dose directly through the buccal mucosa (Stanley et al., 1989; Streisand et al., 1991). Currently approved by the United States Food and Drug Administration for anesthetic premedication and conscious sedation in monitored settings, OTFC has been anecdotally reported to be an effective therapy for cancer-related breakthrough pain (Fine et al., 1991).

The systematic investigation of a new opioid formulation for breakthrough pain is unique. In the absence of previous controlled clinical trials of treatments for breakthrough pain, new methodologies were developed to accomplish this goal. A recent study of OTFC demonstrated the feasibility of a randomized, placebo-controlled, multiple cross-over design (Farrar et al., 1998). The present study applied a novel controlled dose titration methodology to evaluate the safety and efficacy of ascending doses of OTFC as specific therapy for breakthrough pain in cancer patients receiving varied scheduled oral opioid regimens for chronic cancer-related pain. This methodology incorporated blinding and randomization procedures into the evaluation of recurrent pains in the home environment.

2. Methods and materials

This multicenter study evaluated the effects on breakthrough pain produced by ascending doses of OTFC, using random assignment and double-blind drug administration to ensure that the patients and study staff were unaware of the actual dose administered as dose titration ensued. The study was approved by the Institutional Review Boards at each site and all patients gave written consent prior to participation.

2.1. Study population

Adult patients with cancer-related pain were eligible for the study if they (1) were receiving a scheduled oral opioid regimen equivalent to 60–1000 mg oral morphine per day (2) had experienced at least one episode per day of breakthrough pain between 0700 and 1600 h on the 3 days immediately preceding screening, and (3) had achieved at least partial relief of this breakthrough pain by the use of an oral opioid rescue dose. Breakthrough pain was defined as a transitory flare of pain to moderate, severe or excruciating intensity that occurred on a background of chronic pain that was maintained at moderate intensity or less by the fixed schedule opioid regimen. If patients had more than one type of breakthrough pain or had breakthrough pain in more than one location, they were asked to identify one pain as a 'target' breakthrough pain for the study. A standard relative potency table (Jacox et al., 1994) was used to determine the morphine equivalent dose for patients who were receiving an opioid other than morphine.

Patients were excluded from the study if they had a recent history of substance abuse, neurologic or psychiatric impairment sufficient to compromise data collection, any major organ impairment that could increase the risk of supplemental opioids for treating breakthrough pain, or any recent therapy that could potentially alter pain or response to analgesics during the study. Specific exclusion criteria included renal or hepatic function tests greater than three times the upper limit of normal, treatment with strontium-89 within 60 days, and treatment with radiotherapy to a painful site within 30 days prior to the study. Patients who had moderate to severe oral mucositis were also excluded.

2.2. Procedures

Patients who remained eligible following screening proceeded to the two phases of the study: (1) opioid dose

stabilization and baseline data, and (2) OTFC dose titration.

2.2.1. Opioid dose stabilization and baseline data

Baseline data concerning the performance of the patient's usual rescue drug were collected on 2 consecutive days during a period of stable dosing. 'Stable' dosing was defined as at least 3 consecutive days during which the scheduled opioid regimen yielded an average daily pain of moderate severity or less, tolerable opioid side effects, and the need for four or fewer rescue doses. If patients had a history of stable dosing for at least 3 consecutive days prior to screening, baseline data collection about the performance of the usual rescue drug was allowed to proceed immediately after screening. Patients who did not meet the criteria for a stable opioid regimen at the time of screening underwent adjustment of the regimen using a standardized procedure based on widely accepted guidelines for the management of cancer pain (American Pain Society, 1992; Jacox et al., 1994; Levy, 1996). This stabilization period, which could continue for as long as 1 month, was stopped when the criteria for stable dosing were achieved for 3 consecutive days. After stable dosing was achieved, the patients collected baseline data for 2 consecutive days. Patients were allowed 5 working days to identify 2 consecutive baseline days with breakthrough pain that could be assessed between 0700 and 1600 h.

2.2.2. OTFC dose titration

The OTFC dose titration phase followed the baseline data collection. Patients were given multiple OTFC units at a specific dose; only one unit dose was administered at a time. They were instructed to consume up to four separate OTFC units at 15 min intervals to treat a breakthrough pain. The goal of this phase was to gradually increase the size of the OTFC unit dose until the target breakthrough pain could be adequately treated using only a single OTFC unit.

Each day, up to two episodes of breakthrough pain between 0700 and 1600 h could be selected for OTFC treatment. The usual rescue drug was used to treat all other breakthrough pains on these study days. If two breakthrough pains were treated with the OTFC during a single day, a minimum of 2 h was required between the end of treatment for the first and the start of the second.

Once a pain was selected for OTFC treatment, the patient recorded pain data, then consumed an entire OTFC unit, if possible during a period of 15–20 min. To ensure that the drug was tolerated and that the decision to consume another unit was consistent with the protocol, patients were initially required to call the study nurse prior to taking the second or third OTFC unit.

All patients who entered the dose titration phase were randomly assigned to begin treatment with either a 200 or a 400 μg OTFC unit. All units were identical in appearance and both the patient and the investigator were blind to this starting dose. With the option to consume up to four units to treat a breakthrough pain episode, the full starting dose to treat a breakthrough pain could be as high as 800 μg for those randomized to receive the 200 μg unit and 1600 μg for those randomly assigned to receive the 400 μg unit.

The size of the OTFC unit dose could be increased or decreased on successive days. The available OTFC units contained 200, 400, 600, 800, 1200, or 1600 μg of fentanyl citrate. Each increase or decrease consisted of a change to the next step in this sequence of doses. For example, titration for a patient who received the 400 μg OTFC unit would consist of an increase to the 600 μg OTFC unit or a decrease to the 200 μg OTFC unit. When this new unit was used to treat a breakthrough pain, as many as four could be consumed at 15 min intervals, if needed.

The decision to titrate or maintain the dose for another day was made following a daily telephone assessment that evaluated response to the OTFC, including the number of units consumed and a global evaluation of analgesia and side effects. Simple guidelines were developed to encourage consistency in the investigators' judgments concerning dose titration. For example, investigators were encouraged to decrease the size of the OTFC unit if the patient consumed a single unit and experienced unacceptable side effects. Conversely, investigators were encouraged to consider a dose increase if no unacceptable side effects occurred and two or more units were required to provide adequate pain relief for an episode of breakthrough pain. All potential dose changes were discussed with the patient and a request for a change in dose was communicated to the pharmacist only if the patient agreed. New OTFC units were provided each time a decision to change the dose was made.

In contrast to the decision to reduce the dose, which was promptly implemented by the study pharmacist, the request to increase the dose was ignored one-third of the time to create additional uncertainty concerning the actual dose of OTFC. When the study pharmacist received a request to increase the dose, a separate randomization table was consulted that assigned each request into an 'increase dose' or 'ignore request' category. If the request for a dose increase was ignored, the following request was always fulfilled. Combined with the double-blind, random assignment to a starting dose, this second randomization and blinding procedure reduced the likelihood that the patient or investigator would know either the size of the dose or whether it represented a true increase over the prior dose.

The titration process continued until a dose of OTFC was found that provided adequate relief of the target pain on 2 consecutive days without the need to take more than one unit. On each of these days, one or two breakthrough pains could be treated with the OTFC. Patients who could not attain adequate relief of the breakthrough pain with a single 1600 μg dose, the highest strength available, and those who could not be adequately titrated during a maximum of 20 days, were removed from the study.

2.3. Outcome measures

All patients completed a questionnaire that provided detailed information about their persistent pain and breakthrough pains, and both disease-related and demographic information. On each day of the study, patients completed a daily diary that recorded global information about the persistent and breakthrough pain, pain treatments, and changes in medical condition. This information was used to ensure that the underlying pain syndrome remained stable during the study. On the evenings of the 2 baseline days and each OTFC treatment day, patients also recorded a global performance evaluation of the rescue drugs used during the day. These global performance scales ranged from 0 (poor) through 4 (excellent).

The primary outcome data comprised pain scores collected during treatment of one or two episodes of breakthrough pain during both baseline days and the 2 days following successful titration of the OTFC dose. Data collection was similar for all these episodes of breakthrough pain. Immediately before drug administration, patients recorded pain intensity in a study diary using an 11-point numerical scale (0, no pain; 10, pain as bad as you can imagine). Measurements of pain intensity and pain relief were recorded at approximately 15, 30 and 60 min after starting treatment. Breakthrough pains that required more than one OTFC unit were assessed at only 15 min after starting the dose. Pain was again evaluated on the 11-point numerical scale and pain relief was assessed using a four-point categorical scale (0, 'none'; 4, 'complete'). A global impression of the drug's performance, which used a rating from 0 (poor) through 4 (excellent), was recorded once daily. Based on the actual times of assessment recorded by the patients, the 15 min evaluation actually represents an interval of 10–20 min from the start of study drug consumption, the 30 min evaluation represents an interval of 25–35 min, and the 60 min evaluation represents an interval of 50–70 min.

Adverse events were elicited by the study nurse at the time of each patient contact. On the baseline days and the days that the OTFC was assessed, the study nurse inquired specifically about the occurrence of adverse effects related to the drug used to treat the breakthrough pain.

2.4. Data analysis

The scores on the instruments used to acquire pain intensity, pain relief and global performance data were averaged for each patient during each phase of the study. For example, the 15 min pain relief associated with the usual rescue dose during the baseline period was evaluated by averaging the 15 min pain relief scores for all the breakthrough pain episodes assessed during the baseline period (minimum of one per day for 2 days and maximum of two per day for 2 days). This overall pain relief score from each patient was then averaged across patients to yield a pain relief summary score for each phase of the study.

To evaluate pain intensity, pain intensity differences (PID) and the change in pain relief were calculated similarly. For example, the 0–15 min PID was calculated by subtracting the 15 min pain intensity score following consumption of the drug from the pain intensity score immediately prior to drug consumption for each episode of breakthrough pain. These PIDs were averaged within each patient for each study phase, then averaged again across patients. The 0–15 min PID was available for all assessed episodes of breakthrough pain; the 15–30 min PID and the 30–60 min PID were available only for those breakthrough pains evaluated during the 2 days of the baseline period and the 2 days following successful OTFC titration.

Outcome variables collected once daily, such as global performance of rescue drug, were also averaged for each patient within the same phase of the study. Averages of these scores across patients again yielded summary scores for the various phases of the study.

Continuous demographic data, pain severity at screening, log transformed medication level data, outcome data (pain intensity, PID, pain relief, global rating), number of titration increases, number of breakthrough pain episodes per day, and final OTFC dose level were analyzed using two-way analysis of variance, with terms for treatment group, site, and treatment group by site. A separate analysis was done for each phase that included the measurements performed in each phase. The objective was to compare the treatment groups.

Categorical data (gender, race, pain pathophysiology and pain syndrome, completion status) were analyzed with the Cochran Mantel Haenszel General Association Test. The comparisons of treatment groups were performed after stratifying on site. When comparing the two phases for outcome data, and when comparing the first to last OTFC doses, a paired *t*-test (pairing within patient) was used. When comparing the first dose outcome measures across patients, a one way ANOVA was used, with a term for treatment group. Relationship of final dose to type of pain was analyzed with a one-way ANOVA, with a term for type of pain, and the relationship of completion status to type of pain was analyzed using Fisher's Exact Test.

Finally, the association between OTFC dose and opioid effects was analyzed with a linear regression. For all analyses, a (two-sided) P-value < 0.05 was considered statistically significant.

3. Results

Sixty-seven patients who met the eligibility criteria were screened into the study. Two patients did not successfully complete the stabilization phase and never received OTFC. Two other patients began the OTFC titration phase but then experienced a change in pain and opioid requirement, and

were temporarily removed from the study. These two patients were later re-randomized in the study following improvement in their pain syndromes and stabilization. Thus, 65 patients were randomized to the different starting doses of OTFC and provided outcome data for analysis.

3.1. Patient characteristics

The characteristics of the 65 patients are described in Table 1. The mean (±SD) age was 53 ± 12 years. More than half (57%) of the patients were women and 82% were Caucasian. Fifty-five percent had cancers of the breast, colon, head or neck, or lung.

Table 1
Demographic, tumor-related, and pain-related information ($n = 65$)

	Mean ± SD (range)
Age (years)	53 ± 12 (26–74)
Height (cm)	168 ± 11 (150–196)
Weight (kg)	70 ± 21 (27–137)
Sex	*No. (%)*
Male	28 (43)
Female	37 (57)
Race	*No. (%)*
White	53 (82)
Black	5 (8)
Hispanic	7 (1)
Pain etiology (persist)[a]	
Tumor	51 (78)
Treatment	9 (14)
Other	5 (8)
Pain etiology (BT)[b]	
Tumor	51 (78)
Treatment	9 (14)
Other	5 (8)
Pain pathophy (persist)[c]	
Somatic	29 (45)
Visceral	14 (22)
Neuro	22 (34)
Pain pathophy (BT)[d]	
Somatic	28 (43)
Visceral	15 (23)
Neuro	22 (34)
Tumor type	
Breast	17 (26)
Lung	7 (11)
Colon	6 (9)
Head/neck	6 (9)
Other	29 (45)[e]

[a]Pain etiology (related directly to tumor, treatment, or other factors) of the persistent pain.
[b]Pain etiology (related directly to tumor, treatment, or other factors) of the target breakthrough pain.
[c]Inferred pathophysiology of the persistent pain (neuro = neuropathic).
[d]Inferred pathophysiology of the persistent pain (neuro = neuropathic).
[e]Other diagnoses: kidney-3, non-Hodgkins lymphoma-3, sarcoma-3, uterine-3, unknown primary-3, esophageal-2, pancreas-2, melanoma-2, Bartholin's gland carcinoma-1, Hodgkin's lymphoma-1, testicular-1, plasma cell dyscrasia-1, neuroepithelioma-1, liver-1, ovarian-1, prostate-1.

Three-quarters of the patients had persistent pain that could be ascribed to a direct effect of the tumor. In almost all cases, the target breakthrough pain was an acute exacerbation of the persistent pain. At screening, the mean (±SD) severity of the persistent pain (pain on average during the day) was 4.6 ± 2.5 on the 0–10 numeric scale, and the range was 0 to 10. There were no significant differences among treatment sites or between patients randomized to the 200 versus 400 μg OTFC dose on any of these variables, with the exception of pain intensity at screening; this pain rating varied across study sites ($P = 0.004$), but the comparisons between treatment groups were consistent at each site, as indicated by a non-significant treatment-by-center interaction ($P = 0.34$).

Most patients (92%) received controlled-release oral morphine as the opioid administered on a fixed schedule. The rescue opioid varied among short-acting morphine (52%), oxycodone (22%), hydromorphone (12%), hydrocodone (9%), and codeine (5%).

3.2. Baseline period

During the baseline period (that is, after criteria for stable dosing had been met), patients evaluated their regular rescue drug for 2 consecutive days, rating pain and other outcomes for up to two episodes per day and providing a global performance rating for each day. Patients subsequently randomized to the 200 μg OTFC starting dose did not vary from those who received the 400 μg dose in the number of breakthrough pain episodes during the baseline period.

For the purposes of comparison, the doses of all opioids were converted to morphine equivalent milligrams using standard relative potency estimates (Jacox et al., 1994). During the baseline period, the mean (±SD) daily dose of the scheduled opioid was 208 ± 177 mg and the mean (±SD) size of the usual rescue dose was 26 ± 22 mg (Table 2). The mean (±SD) ratio of the rescue dose:total daily dose of the scheduled drug was 0.15 ± 0.09, and the geometric mean was 0.12. The ratio ranged from 0.04 to 0.50; 25 patients (38%) had a ratio less than 0.10 and 15 patients (23%) had a ratio greater than 0.20. Thus, the ratio of rescue dose:total daily dose had a broad distribution that averaged 10–15%. Although there were significant differences in these doses across study sites, there was no treatment-by-center interaction and the comparisons across treatments at the various sites were, therefore, consistent.

Immediately prior to the rescue dose, the mean pain intensity score was approximately 6 on the 0–10 numeric scale. After 60 min, the pain intensity averaged 2.5. Between time 0 and 15 min, the pain intensity lessened by 32% of the total decline in pain; similar reductions in pain intensity occurred during each of the subsequent 15 min periods.

Mean pain relief scores at 15 and 30 min after the rescue

Table 2

Opioid consumption during the baseline period, following opioid stabilization in patients randomized to the 200 μg OTFC starting dose ($n = 32$) and the 400 μg OTFC starting dose ($n = 33$), and the total group ($n = 65$)

	200 μg	400 μg	Total
	No. (%)	No. (%)	No. (%)
Scheduled opioid[a]			
Morphine, long-acting	30 (94)	30 (91)	60 (92)
Hydromorphone	0 (0)	2 (6)	2 (3)
Oxycodone	2 (6)	0 (0)	2 (3)
Methadone	0 (0)	1 (3)	1 (2)
Rescue opioid			
Morphine, short-acting	19 (59)	15 (45)	34 (52)
Oxycodone	6 (19)	8 (24)	14 (22)
Hydromorphone	3 (9)	5 (15)	8 (12)
Hydrocodone	2 (6)	4 (12)6 (9)	6 (9)
Codeine	2 (6)	1 (3)	3 (5)
Opioid dose (mg)[a]	222 ± 173 (60–800)[b*]	195 ± 182 (60–800)[b]	208 ± 177 (60–800)[b]
Rescue dose (mg)	31 ± 27 (5–100)[b*]	21 ± 14 (5–60)[b]	26 ± 22 (5–100)[b]
Ratio of doses[c]	0.16 ± 0.10 (0.04–0.50)[b*]	0.14 ± 0.08 (0.04–0.33)[b]	0.15 ± 0.09 (0.04–0.50)[b]

[a]Total daily dose administered on a fixed schedule.
[b]All opioid doses converted to mg equivalent to morphine using standard relative potencies.
[c]Ratio of rescue dose: fixed schedule dose.
*Data are the mean ± SD (range).

dose were between 1 and 2 on the 0–4 verbal rating scale, which correspond to the descriptors 'slight' to 'moderate' pain relief. At 60 min, the pain relief improved to a mean of 2.5, which corresponds to the range 'moderate' to 'lots' of pain relief. The global performance of the usual rescue drug during the baseline period was 2.0 on the 0–4 verbal rating scale.

There were no significant differences between patients randomized to the 200 μg versus 400 μg starting doses in any of these outcome variables. Again, there were significant differences across study sites, but the treatment-by-center interactions were non-significant.

3.3. OTFC titration phase

Thirty-two patients were randomly assigned to receive the 200 μg OTFC starting dose. Twenty-five (78%) were successfully titrated until a single OTFC unit could adequately treat the breakthrough pain; 5 (16%) withdrew due to adverse events (see below), 1 (3%) withdrew for some other reason, and 1 (3%) could not be successfully treated even after titration to the 1600 μg OTFC unit size. Thirty-three patients were randomly assigned to receive the 400 μg OTFC starting dose. Twenty-three (70%) successfully completed the OTFC titration phase; 3 (9%) withdrew due to adverse events (see below), 3 (9%) withdrew for some other reason, and 4 (12%) could not be successfully treated at the 1600 μg OTFC unit size. There was no significant difference in the completion rate between randomly assigned groups. The category, 'withdrawal for other reasons,' included patients who left the study due to the cessation of breakthrough pain, chemotherapy, change in the fixed schedule drug, and refusal related to incomplete pain relief.

3.3.1. Dose response

Differences in the responses to the lower initial dose and higher last dose, or to the 200 and 400 μg starting dose, would indicate a dose response relationship and suggest the adequacy of the blinding procedures and the sensitivity of the methodology. An analysis of pain scores following the first and last doses of OTFC in all patients who underwent dose escalation demonstrated that the higher dose produced a significantly greater mean pain intensity difference ($P < 0.002$) and pain relief ($P < 0.0001$) at the 15 min assessment than the lower dose, as well as a better global rating ($P < 0.0001$).

A dose response was similarly supported by the finding that successfully treated patients who were randomized to the 200 μg dose required more dose increases than those randomized to the 400 μg dose (mean [±SD] of 1.56 ± 1.69 for the 200 μg dose versus 0.70 ± 0.88 for the 400 μg dose, $P = 0.051$). During the titration process, no patient required a dose decrement.

Finally, dose response was suggested by the patients' reaction to the blinding procedures for dose escalation. According to the randomization schedule, one-third of orders to increase the dose were ignored. Eleven of the 48 successfully titrated patients had orders for dose escalation ignored a total of 15 times. Of these 15 times, only three reported that the same dose was successful on the subsequent trial and 12 (80%) required further dose escalation to find an effective dose.

In contrast to the latter findings, analysis of pain scores

following the first dose failed to reveal any significant differences between the 200 and the 400 μg dose. Although this outcome does not support a dose response relationship, it may be explained by the large number of patients who attained satisfactory analgesia after the lower starting dose. Approximately one-third of the patients who received the 200 μg dose reported that this dose was satisfactory. It is likely that many of the patients who received 400 μg would have responded to a lower dose and could not demonstrate much additional analgesia from that part of the dose in excess of 200 μg.

3.3.2. Drug exposure and other analgesic outcomes

Altogether, the 65 patients consumed 913 OTFC units to treat 489 breakthrough pains. As noted previously, OTFC unit dose sizes varied between 200 and 1600 μg, but patients could use up to four units to treat an episode of breakthrough pain. Twenty-six patients (40%) used only 200 or 400 μg doses to treat all episodes, and nine patients (15%) used doses of 3200–6400 μg to treat at least one episode. Similarly, 132 episodes (31%) were treated with a total dose of 200 or 400 μg, and 58 episodes (12%) were treated with a total dose of 3200–6400 μg.

The mean (±SD) dose of OTFC following successful titration was 640 ± 374 μg for those patients randomized to the 200 μg starting dose and 548 ± 202 μg for those who received the 400 μg starting dose. This difference was not significant ($P = 0.13$). Neither the final dose nor the likelihood of a successful titration was influenced by any characteristic of the patient, including type of pain. Most notably, a neuropathic mechanism did not reduce the likelihood of a favorable response to the OTFC.

In contrast to the usual rescue drug, there was no relationship between the successful dose of OTFC and the scheduled dose of opioid. The 200 or 400 μg dose was effective for more than half (54%) of the successful patients, irrespective of the total daily dose of the scheduled drug. Those who could not be successfully titrated despite escalation to the 1600 μg OTFC dose did not have a scheduled opioid dose higher than the successful patients; two of these unsuccessful patients received total daily doses (morphine 60 and 120 μg, respectively) that were substantially below the mean consumption, and only one patient received a dose that was >1 standard deviation above this mean dose.

The 48 patients who were successfully titrated assessed the response to a single OTFC unit during treatment of up to two breakthrough pains per day for each of 2 days, and provided a global performance rating for each day. Like the assessment prior to the usual rescue dose, the mean pain intensity immediately before the OTFC dose was approximately 6 on the 0–10 numeric scale. After 60 min, the pain intensity averaged 1.5. The reduction in pain intensity during the 0–15 min time period was 56% of the total pain intensity decline.

Mean pain relief scores at 15 and 30 min after the OTFC dose were 2.1 and 2.5, respectively, where 2 corresponds to the descriptor 'moderate' and 3 corresponds to the descriptor 'lots' of pain relief. At 60 min, the pain relief increased to a mean of 3.1. The global performance of the OTFC during the 2 successful treatment days was 2.9 on the 0–4 verbal rating scale.

With the exception of a single pain intensity difference recorded at the 60 min time point, there were no significant differences between patients randomized to the 200 versus 400 μg starting doses in any of these outcome variables. Although there were significant differences across study sites for some of the variables, in no case was the treatment-by-center interaction significant.

3.3.3. Time-action characteristics of usual rescue drug versus OTFC

A comparison of the time-action relationships of the usual rescue dose and the OTFC in successfully titrated patients ($n = 48$) also demonstrated a more rapid onset of analgesia following OTFC treatment (Fig. 1). In this subgroup, the decline in pain intensity during the initial 15 min period was 56% of the total pain reduction following OTFC and 32% of the total following the usual rescue dose ($P < 0.0001$). The amount of pain relief during this initial period was 65% of total pain relief for OTFC and 46% of total pain relief for the usual rescue dose ($P < 0.0001$).

3.3.4. Adverse events

During the OTFC titration phase, ten patients withdrew from the study due to adverse event. Two patients temporarily withdrew due to increasing intensity of the persistent pain, but were allowed to enroll a second time after their pain stabilized. Two patients withdrew due to events, i.e. an episode of dizziness, hallucinations, and body numbness, and an episode of dry mouth, headache, dizziness, and somnolence, judged by the investigators involved as 'probably' related to the OTFC, and two other patients withdrew due to events in an episode of somnolence associated with unrelieved pain and an episode of nausea and vomiting is judged to be 'possibly' related. The three other adverse events preceding withdrawal from the study were serious medical complications related to the underlying disease and unrelated to the OTFC; all resulted in hospitalization and one led to a patient death.

There were four other serious adverse events during the study, each of which resulted in hospitalization but did not require withdrawal from the study. One of these events, an episode of severe nausea, constipation, and dehydration, was considered to be 'possibly' related to the OTFC by the investigator involved. The others represented unrelated complications attributable to the underlying disease or associated comorbidity.

The side effects associated with the OTFC were typical opioid-related events. On the days that any OTFC was taken, side effects that occurred with a frequency of ≥5% and were considered by the investigator to be 'possibly,' 'probably,' or 'almost certainly' associated with the study

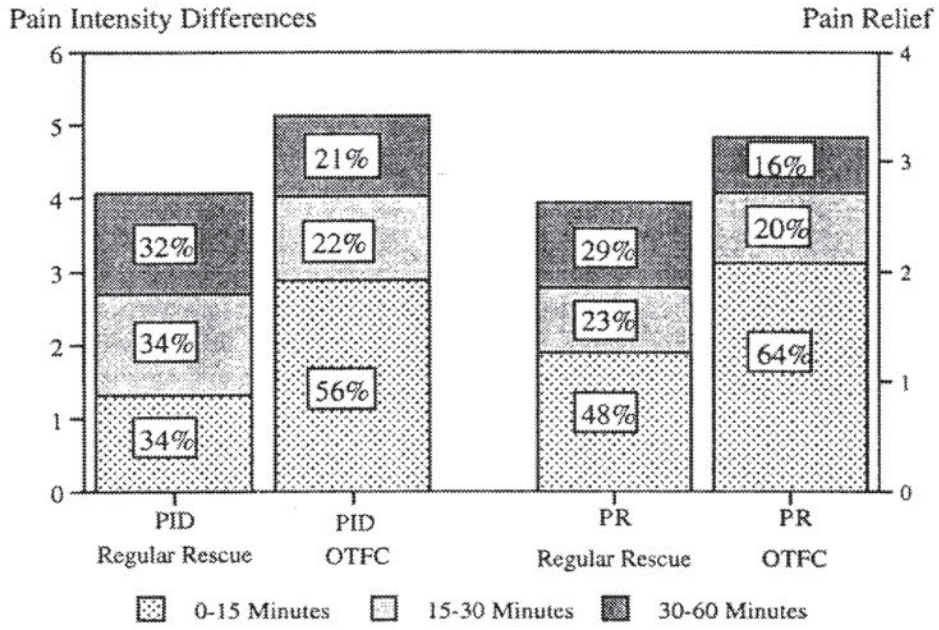

Fig. 1. Change over time in mean pain intensity and mean pain relief produced by OTFC and the usual rescue dose in all patients who were successfully titrated to an effective OTFC dose and assessed their usual rescue drug during the baseline period ($n = 48$).

drug comprised somnolence (28%), dizziness (14%), nausea (10%) and headache (5%). During the last 2 days of OTFC administration, when the OTFC dose had been appropriately titrated, the side effects that occurred with a frequency of ≥5% and were considered to be at least 'possibly' related to the study drug again included somnolence (15%), dizziness (6%), and nausea (5%).

To assess the dose response for these non-analgesic effects, an 'opioid effect score' was calculated as the total number of adverse events perceived by the investigators as 'possibly,' 'probably,' or 'almost certainly' associated with the study drug and occurring on the days that OTFC was consumed. Numerous potential adverse effects were included in the score: asthenia, confusion, constipation, dizziness, dry mouth, dyspepsia, hypotension, nausea, nausea and vomiting, somnolence, sweating, syncope, urinary retention, vasodilation, vertigo, and vomiting. The possible range was 0 to 16 symptoms. The mean (±SD) score of those patients whose highest OTFC unit dose was 200 μg was 0.25 ± 0.62. The 400, 600, 800 and 1600 μg unit doses were associated with scores of 0.48 ± 0.98, 0.93 ± 0.92, 1.00 ± 1.53, and 1.25 ± 1.28, respectively. Despite a mean score of 0 for the three patients who consumed the 1200 μg unit dose, there was a trend towards statistical significance in the association between dose and these non-analgesic opioid effects ($P = 0.06$), further indicating a dose response relationship.

4. Discussion

Breakthrough pain is a highly prevalent clinical phenomenon that undermines the overall benefit of opioid therapy for chronic cancer pain (Mercadante et al., 1992; Bruera et al., 1995). Clinicians who manage cancer pain recognize the importance of specific interventions for the management of breakthrough pain, and commonly implement recommended guidelines for the use of a rescue drug in combination with scheduled opioid therapy (Jacox et al., 1994; Levy, 1996). These recommendations, which are based entirely on anecdotal experience, favor the selection of a short-acting opioid at a dose proportionate to the total daily dose.

Given the widespread use of rescue dosing, the lack of systematic clinical investigation of breakthrough pain and its therapies is remarkable. There have been no drugs or drug formulations developed specifically for breakthrough pain and, prior to this study, there have been no controlled clinical trials that evaluate the pharmacology of those drugs and formulations conventionally used for this indication.

The difficulties inherent in studying breakthrough pain probably contribute to the lack of data. Breakthrough pain is extremely heterogeneous (Portenoy and Hagen, 1990), and may vary in frequency, onset and duration, severity, quality, etiology and pathophysiology, and impact. It is only sometimes predictable and can vary from episode to episode in the same patient. The methodological challenge in studying a highly variable, subjective phenomenon that may or may not occur during any planned assessment period is evident.

OTFC is the first drug therapy undergoing investigation as a treatment for breakthrough pain, and the first to be evaluated in controlled clinical trials (Farrar et al., 1998).

The present study evaluated the safety and efficacy of ascending doses of OTFC using a novel controlled dose titration methodology that applied blinding and randomization procedures to the evaluation of recurrent pains in the home environment. The results are, therefore, informative in terms of both the formulation itself and the methodological considerations that must be addressed in future therapeutic trials that target breakthrough pain.

OTFC is a novel formulation of the highly potent and lipophilic synthetic opioid, fentanyl citrate. In the OTFC formulation, fentanyl is incorporated in a sweetened matrix, which is dissolved in the mouth. Part of the dose is absorbed transmucosally and part is swallowed, yielding pharmacokinetics unique to the formulation (Stanley et al., 1989; Streisand et al., 1991). Based on these kinetics and an anecdotal clinical experience (Fine et al., 1991), it has been postulated that OTFC may offer characteristics, such as a rapid onset and short duration, that favors its use as an intervention for breakthrough pain.

The present study used two separate blinding and randomization procedures to ensure that neither the patient nor the investigator knew the actual dose administered during the study period. Dose response relationships were found for both analgesic outcomes and the occurrence of non-analgesic effects, suggesting that the methodology was sensitive to opioid effects. The results demonstrated that 74% of patients were able to identify a safe and effective dose of OTFC, which could adequately treat a target breakthrough pain with a single unit. In contrast to expectations, there was no relationship between the total daily dose of the scheduled opioid regimen and the dose of OTFC required to effectively manage the breakthrough pain. The time-action relationship of the OTFC also differed from the usual oral rescue drug in providing a significantly greater analgesic effect during the initial 15 min after the dose. Adverse effects of the OTFC were generally tolerable and typically opioid-related, specifically somnolence, nausea, and dizziness.

This study was not designed to validly compare the analgesic efficacy of OTFC with the usual rescue drug, and additional randomized trials will be necessary to confirm the observation that OTFC yielded more rapid and more complete analgesia, and better patient-rated global performance, than the usual rescue administered during an optimally titrated opioid regimen. Based on the results of this study, it may be hypothesized that OTFC produces better outcomes in at least some patients and, further, that it may be the more rapid onset of effect produced by transmucosal drug absorption that is the major factor that determines this better outcome.

Current guidelines for opioid therapy recommend that the size of an oral or parenteral rescue dose should be calculated as a proportion of the dose administered on a scheduled basis (Portenoy and Hagen, 1990; American Pain Society, 1992; Jacox et al., 1994; Levy, 1996). This guideline, which is based on anecdotal observations, led to the expectation of a relationship between the OTFC dose and the total daily opioid dose. For unknown reasons, this relationship was not found. Additional studies will be needed to confirm this finding and explore potential explanations. For the present, recommendations to begin OTFC dosing with the smallest dosage size (200 μg) and then titrate, are prudent. Since the dose required to treat a breakthrough pain may be related to the duration of the pain, future studies should better define the temporal relations of the target breakthrough as a possible covariate that may explain some aspect of the dose response relationships.

This study illustrates the potential for investigation of breakthrough pain using controlled trials methodology. The feasibility of blinding and randomization procedures in studies of recurrent pains in the home environment has been well demonstrated in headache trials (Schachtel et al., 1991). The present study confirms that this approach is also possible in medically-ill cancer patients with chronic pain and intermittent breakthrough pain. The use of an opioid stabilization period presumably yielded more reliable baseline data and the use of graded OTFC starting doses provided a means to evaluate the sensitivity of the methodology to drug effects (Max and Portenoy, 1993). The assessment of multiple pains yielded more experience with the study drug and more outcome data, and the evaluation of pain characteristics as potential covariates allowed secondary analyses that could have yielded clinically important information.

Some limitations in the design are also apparent, however, and should be addressed in future studies. As noted previously, the study was not intended to validly compare analgesic efficacy of OTFC and the usual rescue dose, and this comparison must be considered tentative given the potential for an order effect and differential placebo effects in the two treatments. However, the highly significant differences between the regular rescue and OTFC are intriguing and should be investigated further. Although the assessment of multiple breakthrough pains presumably increased the stability of the data, it could also introduce carryover effects, which could be pharmacokinetic or conditioned. Systematic evaluation of this possibility may also be warranted in future studies. Finally, the use of the usual rescue drug during the OTFC dose titration period to treat pains that could not be treated with the OTFC, could have potentially altered the expectations about the OTFC and introduced a systematic bias in the responses. Again, future studies may wish to consider a separate drug for the rescue doses that are not investigated.

These limitations notwithstanding, the present study represents an important step in applying analgesic trials methodology to the important phenomenon of breakthrough pain. The data suggest that OTFC can be a safe and effective drug for this problem. Further studies into its dose response relationships, pharmacokinetic-pharmacodynamic relationships, and comparative benefits and risks in diverse patients and varied types of breakthrough pain are warranted.

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EXHIBIT 4

A Randomized, Placebo-controlled Study of Fentanyl Buccal Tablet for Breakthrough Pain in Opioid-treated Patients With Cancer

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Objectives: Cancer-related breakthrough pain (BTP) is typically managed with a short-acting oral opioid, taken as needed during a fixed-schedule opioid regimen. The conventional approach may not provide the onset of analgesia required for BTP for many patients, because the onset of analgesia with short-acting opioids lags behind the time course of the majority of episodes of BTP. The fentanyl buccal tablet (FBT) employs a novel delivery system that enhances the rate and extent of absorption of fentanyl through the buccal mucosa. This double-blind, randomized, placebo-controlled study evaluated the efficacy, safety, and tolerability of FBT in opioid-treated patients with cancer-related BTP.

Methods: After an open-label titration (N = 123) to identify an effective FBT dose to treat BTP episodes, 77 patients were randomly assigned to 1 of 18 prespecified dose sequences of 10 tablets (7 FBT and 3 placebo). Pain intensity, pain relief (PR), and global performance of the medication were recorded at regular time intervals between 15 and 60 minutes. Pain intensity differences (PID), the summed PID (SPID), and summed total PR were calculated. The SPID at 30 minutes ($SPID_{30}$) was the primary efficacy variable. Adverse events were reported.

Results: Sixty-five percent (80/123) of patients were titrated to an effective dose. The mean (SE) $SPID_{30}$ for FBT was 3.0 ± 0.12 versus 1.8 ± 0.18 for placebo ($P < 0.0001$). Measures of PR, PID, SPID, summed total PR, and patient ratings of global performance of medication significantly favored FBT over placebo at all time points. Adverse events were typical of opioid drugs. Poor oral tolerability was noted in 2 patients.

Conclusions: FBT is efficacious and safe in the treatment of cancer-related BTP.

Key Words: fentanyl buccal tablet, rapid-onset opioid, breakthrough pain, cancer pain

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Breakthrough pain (BTP) is a transitory exacerbation of pain that occurs on a background of otherwise controlled persistent pain.[1,2] Although there has been some debate about nomenclature, particularly the use of related terms such as "incident pain" and "episodic pain,"[3,4] the high prevalence and negative impact of these transitory pains are now well established. The prevalence of cancer-related BTP is 50% to 90%[1,2,5–9]; among patients with cancer, BTP has been associated with more severe chronic pain,[5,6] relatively more impairment in physical functioning and greater psychologic distress,[5,6] reduced responsiveness to opioids,[10,11] and an increased economic burden.[12] Little is known about the epidemiology of BTP in populations with chronic pain unrelated to cancer, but a recent survey suggests that the prevalence and characteristics of these pains among patients treated at pain clinics are similar to cancer-related BTP.[13]

BTP is a significant clinical problem and data support a consensus that BTP should be independently assessed and treated.[14,15] The most common approach involves access to a "rescue," or supplemental, medication—a short-acting opioid provided in combination with the fixed-schedule opioid regimen. This approach is widely used in the management of cancer-related BTP and seems to be appropriate for selected patients with chronic pain of other types.

The effectiveness of oral rescue drugs in the management of BTP in opioid-treated patients with chronic pain has not been adequately evaluated. Some surveys of cancer patients suggest that the availability of a short-acting opioid does not prevent the adverse consequences of BTP in most patients.[5] The typical characteristics of BTP, particularly the fact that the pain peaks within minutes,[1,2,5,7,8] suggest that responsiveness to an oral drug may be less than optimal because the onset of analgesia may follow the peak of the target pain. The potential usefulness of a nonparenteral drug for BTP with a faster onset of effect was the rationale for the development of oral transmucosal fentanyl citrate (OTFC) as a treatment for BTP. Controlled studies showed that this formulation could provide analgesia

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at 15 minutes.[16] Efforts are now underway to develop other nonparenteral opioid formulations that could provide more rapid, and possibly more effective, relief of BTP.

The fentanyl buccal tablet (FBT) incorporates a novel drug delivery platform, OraVescent technology, which employs an effervescence reaction to enhance fentanyl absorption through the buccal mucosa and facilitate rapid systemic exposure to the analgesic. Transient pH changes accompany the effervescence reaction, and increase both the rate of tablet dissolution (at a lower pH) and membrane permeation (at a higher pH) of fentanyl.[17,18] In vitro studies show that absorption may also be influenced by other changes thought to occur as a result of the effervescence reaction, including thinning of the mucus layer and loosening of the intercellular tight junctions.[17–19] In a previous study of the bioavailability and pharmacokinetics of FBT compared with OTFC, a larger proportion of FBT was absorbed transmucosally (48%) compared with OTFC (22%) and the T_{max} was earlier after administration of FBT (47 min) than OTFC (91 min).[20] This is the first controlled clinical study designed to evaluate the efficacy, safety, and tolerability of FBT in opioid-treated patients with chronic pain associated with cancer.

MATERIALS AND METHODS

Patient Population

Opioid-treated adult patients ($\geq$ 18 y old) with chronic cancer pain who experienced 1-4 BTP episodes per day were potentially eligible for participation in the study. Patients had to be receiving oral morphine at 60 to 1000 mg/d or an equivalent dose of an alternative oral opioid or 50 to 300 μg/h of transdermal fentanyl for at least 1 week. BTP had to be adequately controlled with a stable dose of a short-acting oral opioid. All patients had a histologically documented diagnosis of a malignant solid tumor or a hematologic malignancy, an Eastern Cooperative Oncology Group performance status rating of $\leq$2,[21] and a life expectancy of $\geq$ 3 months.

Patients were excluded if they were receiving intrathecal opioids; were experiencing mucositis/stomatitis of grade 2 or greater, as defined by the common terminology criteria for adverse events,[22] or had any other condition that could influence tolerability or absorption of FBT across the buccal mucosa; were female and pregnant or lactating; had sleep apnea, active brain metastases with increased intracranial pressure, chronic obstructive pulmonary disease, impaired renal or hepatic function, or significant bradyarrhythmia due to underlying heart disease; or if the primary source of BTP was not cancer-related.

Procedures

This was a randomized, double-blind, placebo-controlled study conducted from November 2003 to December 2004 in 32 outpatient sites. Each site obtained Institutional Review Board approval and each patient provided written informed consent.

An initial screening visit was carried out to collect medical history, perform physical and neurologic examinations, and obtain a clinical laboratory evaluation. Patients who remained eligible entered an open-label titration phase to establish an effective dose of FBT for use in the double-blind phase. Before the first administration, patients were told to place FBT between cheek and gum above a molar and to allow the tablet to dissolve within 15 minutes. Patients were asked to refrain from using their supplemental medication for at least 30 minutes after FBT administration.

To commence the titration phase, patients received a test dose (100 μg) at the study site and were observed for 2 hours to determine tolerability (BTP did not need to be present). The remainder of the titration phase and the double-blind phase proceeded in the patient's home, with frequent monitoring by telephone. For use during the titration phase, FBT tablets were available in 100, 200, 400, 600, and 800 μg doses. Patients were instructed to wait until a BTP episode began, record a baseline pain intensity (PI) score (see below), and then try an initial 100 μg dose of FBT. If the initial dose did not provide satisfactory pain relief (PR) within 30 minutes, patients could use their nonstudy supplemental drug, if needed. The next BTP episode that could be treated had to occur at least 4 hours after administration of the study drug or any supplemental medication. If the initial 100 μg tablet strength did not provide satisfactory relief and adverse effects were tolerable, the patient advanced to the next higher tablet strength when the next BTP episode was treated. Ineffective response with this higher dose was again followed by titration to the next higher tablet strength. Titration in this way continued through the available dosages of FBT. If a dose of FBT provided satisfactory relief, the patient treated the following BTP episode with the same dose.

Patients could proceed to the double-blind phase of the study when a dose provided satisfactory relief within 30 minutes, without unacceptable adverse effects, during the 2 consecutive BTP episodes. This dose was used throughout the double-blind period. Patients discontinued the study if titration to the highest dose (800 μg) did not yield satisfactory PR or FBT produced unacceptable adverse effects.

In the double-blind phase, patients were randomly assigned to 1 of 18 prespecified dose sequences of 10 tablets (7 FBT and 3 placebo). Patients and investigators were blinded to the order in which FBT and placebo tablets were taken to treat successive target BTP episodes. All 10 doses were to be taken within a 21-day period, with a maximum of 4 episodes treated per day.

The procedures that were followed with each dose of study medication during the double-blind phase were similar to those used during the titration phase, except for repeated data collection after administration of FBT or placebo. Patients were instructed to obtain a baseline PI measurement when a BTP episode began. FBT or placebo was then administered. PI and PR were recorded at 15, 30, 45, and 60 minutes thereafter. PI was measured using

an 11-point numeric scale, where 0 = no pain and 10 = worst pain. PR was noted using a 5-point numeric scale, where 0 = none and 4 = complete. Patient rating of global medication performance (GMP) was recorded at 30 and 60 minutes using a 5-point scale, where 0 = poor and 4 = excellent.

Throughout the study, patients could use their prior supplemental drug to treat any BTP episode that did not respond within 30 minutes after FBT or placebo administration. The prior drug also could be taken to treat any BTP episodes in excess of 4 per day, and to treat any episode that occurred < 4 hours after any rescue medication was administered for a previous episode.

Patients could record adverse events (AEs) after each dose and also were queried on AEs at clinical visits scheduled at the completion of each phase. AEs reported include those reported during the titration and double-blind phases. The AE data could not be attributed to the treatment received since patients had received both active treatment and placebo, often during the same day. All normal or abnormal findings on the oral mucosal examinations at visits 1, 2, and 4 were recorded. Any change was noted at subsequent visits and the clinical significance of any abnormal findings was judged. At the final visit, patients also underwent a second physical examination and clinical laboratory assessment.

Statistical Analysis

The difference between each PI measurement after drug administration and the PI value immediately before drug administration [PI difference (PID)] was calculated and the summed PID (SPID) was determined at each time point as an indicator of cumulative analgesia by time after administration of FBT or placebo. The SPID at 30 minutes ($SPID_{30}$) was the primary efficacy measure. To provide a $\geq 95\%$ power to detect a treatment difference of 1.4 between FBT and placebo in the primary efficacy variable, $SPID_{30}$, approximately 63 patients were required for the double-blind phase of the study. Secondary efficacy variables included PR and PID at each time point after dosing; total PR (TOTPAR) at each time point, defined as the sum of PR scores at time points post dose; GMP assessment; and incidence of standard supplemental medication use both after placebo and after FBT administration. In addition, the proportion of episodes in which there was a $\geq 33\%$ or a $\geq 50\%$ improvement in PI scores at each time point was analyzed.

The double-blind safety analysis set included those patients who received one or more doses of FBT during the double-blind treatment period of the study. The efficacy-evaluable population was defined as all patients who received at least one FBT treatment and one placebo during the double-blind phase and had recorded a pretreatment PI score for each episode of BTP. A repeated measure analysis of variance, with treatment and center as fixed factors and subject as a random factor, was used to evaluate the difference between FBT and placebo for the summed outcome variables (SPID and TOTPAR). The 1-sample Wilcoxon signed rank test was used for PID, PR, and GMP. Least-squares (LS) mean and the standard error (SE) of the LS mean are reported for the SPID and TOTPAR variables. For binary outcomes, including use of supplemental medication and percent-improvement criteria, point estimates, and confidence intervals (CIs) for relative risk of attaining the outcome were calculated.

RESULTS

Of the 139 patients screened for the study, 123 were enrolled in the titration phase (Fig. 1). Of the 46 patients who discontinued from the titration phase, 20 did so because of lack of efficacy at the highest tolerated dose, 12 withdrew because of AEs, and the remainder withdrew consent, were lost to follow-up, or had another reason to discontinue. Eighty (65%) patients identified an effective FBT dose during the titration phase and 77 were randomized to a treatment sequence in the double-blind

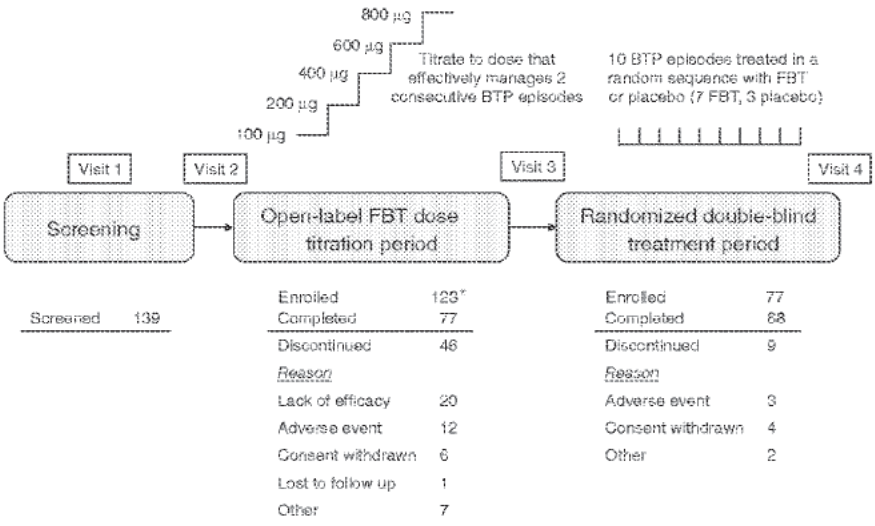

FIGURE 1. Study flow diagram and patient disposition. *Enrolled in the titration period and evaluated for safety and tolerability.

TABLE 1. Patient Demographics in the Overall Population and in the Double-blind Phase

	Overall N = 123	Double-blind n = 77
Female, n (%)	56 (46)	35 (45)
Weight, kg, mean ± SD	74.7 ± 18.5	75.5 ± 17.9
Height, cm, mean ± SD	169.7 ± 11.1	170.1 ± 11.1
Age, y, mean ± SD	58.0 ± 12.6	57.5 ± 13.6
Race, n (%)		
White	109 (89)	68 (88)
Black	2 (2)	1 (1)
Other	12 (10)	8 (10)
Pain pathophysiology, n (%)		
Nociceptive	68 (55)	36 (47)
Neuropathic	23 (19)	16 (21)
Mixed	32 (26)	25 (32)

SD indicates standard deviation.

phase. Nine of these 77 patients discontinued during the double-blind phase, 3 because of AEs and 6 because of withdrawn consent or other reasons. Of the 72 patients who met the criteria to be included in the efficacy-evaluable population, 68 completed the study.

The characteristics of the enrolled patients are described in Table 1. The demographics and pain pathophysiologies for the 77 patients who entered the double-blind phase were similar to the overall population. In the overall population, most patients were receiving fixed-schedule regimens of morphine, oxycodone, or fentanyl (Table 2). The mean (± SD) daily dose of oral opioid regimens was 229.1 ± 1.4 morphine equivalent mg, and the mean daily dose of transdermal fentanyl was 85.7 ± 37.6 μg/h. The mean dose of supplemental medication taken before entry into the study was 20.2 ± 20.3 morphine equivalent mg. In the efficacy-evaluable population, the mean (± SD) daily dose of oral opioid regimens was 208.7 ± 558.2 morphine equivalent mg, and the mean dose of supplemental medication taken before entry into the study was 21.0 ± 23.4 morphine equivalent mg.

TABLE 2. Around-the-clock and Supplemental Medication (N = 123)

ATC medication, mg/d of oral morphine equivalents, mean ± SD	213.5 ± 461.9
Distribution of ATC opioid usage, n (%)	
Fentanyl (oral)	2 (2)
Fentanyl (transdermal)	33 (28)
Methadone	9 (8)
Morphine	40 (34)
Oxycodone	42 (36)
Vicodin	8 (7)
Other	12 (10)
Supplemental medication, mg/d of oral morphine equivalents, mean ± SD	20.2 ± 20.3
Distribution of supplemental opioid usage, n (%)	
Hydrocodone	7 (7)
Hydromorphone	11 (11)
Morphine	18 (17)
Oxycodone	13 (13)
Oxycodone/acetaminophen	25 (24)
Vicodin	22 (21)
Other	8 (8)

For the ATC and supplemental medications, the category "other" denotes opioids taken by < 5% of patients, including ATC medications (codeine/acetaminophen, hydrocodone, hydromorphone, meperidine, meperidine/promethazine, oxycodone/acetaminophen, propoxyphene, and propoxyphene/acetaminophen) and supplemental medications (codeine/acetaminophen, fentanyl citrate, hydrocodone/ibuprofen, meperidine, methadone, and propoxyphene/acetaminophen). Patients may have reported more than 1 drug for ATC and supplemental medications.

SD indicates standard deviation.

Efficacy

For the 77 patients who entered the double-blind phase, the effective FBT dose identified during the titration phase was 100 μg for 12 patients, 200 μg for 11 patients, 400 μg for 20 patients, 600 μg for 10 patients, and 800 μg for 24 patients. There seemed to be no relationship between effective FBT dose and either the dose of the baseline opioid regimen or the supplemental opioid taken at the start of the study.

For the efficacy-evaluable population, a total of 493 BTP episodes treated with FBT and 208 episodes with placebo were observed. Before either FBT or placebo administration, the mean (± SE) PI was 6.9 ± 0.19, which decreased by 2.3 ± 0.2 and 1.4 ± 0.2 points with FBT and placebo, respectively, at 30 minutes. As depicted in Figure 2, the mean (± SE) PID scores and PR scores at each time point were significantly higher for FBT than for placebo, as were the mean (± SE) SPID and TOTPAR scores (for all comparisons, $P < 0.003$ for the 15-min time point and $P \leq 0.0001$ for the 30, 45, and 60 min time points). The $SPID_{30}$ (LS mean ± SEM) was 3.0 ± 0.12 for FBT doses and 1.8 ± 0.18 for placebo doses ($P < 0.0001$; 95% CI of the difference, 0.83-1.62).

Clinically significant improvements in pain scores ($\geq 33\%$ and $\geq 50\%$ reductions) were produced in a larger percentage of FBT-treated episodes than placebo-treated episodes for all time points (Table 3). As early as 15 minutes after treatment, a higher proportion of FBT-treated episodes was characterized by $\geq 33\%$ improvement than episodes in which placebo was administered (13% vs. 9%, $P = 0.045$). At 30 minutes, a $\geq 33\%$ improvement was reported in 48% of FBT-treated BTP episodes versus 29% of episodes in which placebo was received ($P < 0.0001$), and a $\geq 50\%$ reduction was reported in 24% of the episodes treated with FBT versus 16% of episodes in which placebo was received ($P = 0.0023$).

Similarly, GMP ratings for FBT were superior to placebo at both 30 and 60 minutes. The mean values for patients' assessments of FBT and placebo at 30 and 60 minutes were 1.4 versus 0.9 ($P < 0.0001$) and 2.1 versus 1.3 ($P < 0.0001$), respectively. The scores show a shift toward greater satisfaction with FBT from 30 to 60 minutes, indicating a continued improvement over time. Indeed, for 35% of FBT-treated episodes, the GMP at 60 min was rated "very good" or "excellent."

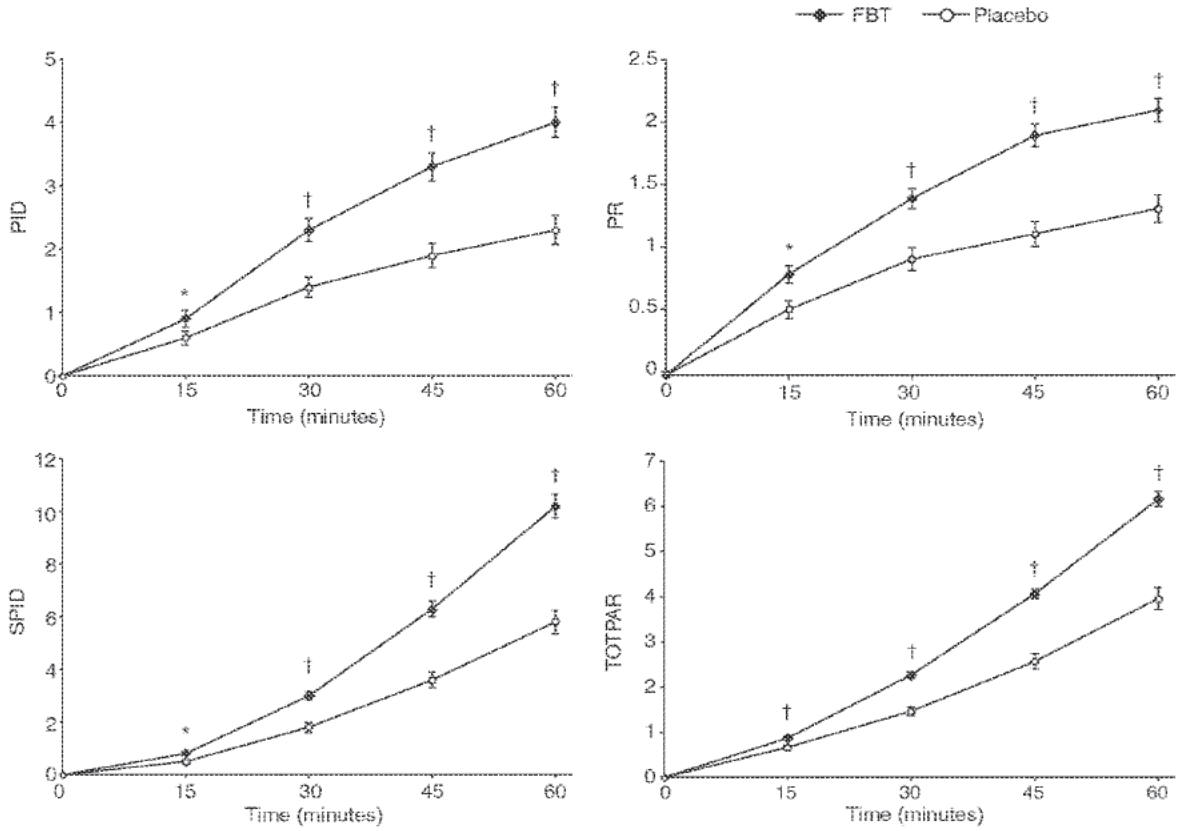

FIGURE 2. PID, PR, SPID, and TOTPAR scores after FBT treatment and placebo administration (mean ± SE is reported for PID and PR, LS mean ± SE of the LS mean for SPID and TOTPAR). *$P<0.003$, †$P \leq 0.0001$.

During BTP episodes in which patients received placebo, patients were more likely to require supplemental medication than during BTP episodes treated with FBT. Supplemental medication was used in 23% of episodes treated with FBT versus 50% of episodes with placebo (relative risk ratio: 0.47; 95% CI, 0.37-0.60).

There was no relationship between efficacy of FBT and age, sex, race, BMI, or type of BTP. However, patients with predominantly neuropathic pain and mixed (neuropathic and nociceptive) pain showed slightly better efficacy as determined by the mean $SPID_{60}$ compared with patients with nociceptive pain. The mean $SPID_{60}$ difference after treatment with FBT was 5.3 for patients with predominantly neuropathic pain and those with mixed pain, and 3.1 for patients with nociceptive pain.

Safety

The most commonly reported AEs were those associated with opioid use: nausea, vomiting, dizziness, constipation, and somnolence (Table 4). Most of these AEs were mild to moderate in severity. Four percent of patients withdrew from the study as a result of nausea

TABLE 3. Number (%) of Responder Episodes With ≥ 33% and ≥ 50% Improvement of Pain Intensity

	Percent Improvement of Pain Intensity Score			
	≥ 33%		≥ 50%	
Time Point	FBT	Placebo	FBT	Placebo
15 min	69 (13)*	20 (9)	44 (8)	13 (6)
30 min	240 (48)†	61 (29)	122 (24)*	34 (16)
45 min	352 (71)†	93 (44)	253 (51)†	52 (25)
60 min	373 (75)†	100 (48)	319 (64)†	74 (35)

FBT n = 493, placebo n = 208.
*$P < 0.05$; †$P < 0.0001$ vs. placebo at the respective time point.

TABLE 4. AEs Reported in >5% of the Population (N = 123)

AE	n (%)
Nausea	27 (22)
Dizziness	27 (22)
Headache	18 (15)
Fatigue	15 (12)
Vomiting	13 (11)
Somnolence	12 (10)
Constipation	10 (8)
Asthenia	9 (7)

This table includes AEs reported in the open-label titration and the double-blind phases of the study.

and/or vomiting, and 2% withdrew because of dizziness. Two (2%) patients had application site ulcers of the oral mucosa that were considered by the investigator to be definitely related or probably related to study drug administration during the dose-titration period; these AEs led to withdrawal from the study. There were no reports of respiratory depression during the titration or double-blind phases. Eleven percent of patients experienced at least 1 serious AE. All serious AEs were deemed related to the patients' underlying conditions. Seven deaths attributable to disease progression occurred during the study.

DISCUSSION

Studies have established that BTP is highly prevalent in the cancer population and negatively impacts patient comfort, functioning, and cost of care.[1,4–9,12] The administration of a short-acting opioid on an as-needed basis (ie, a rescue drug) is a widely accepted approach to the management of this phenomenon.[2,14,15] Although most BTP episodes peak within 30 minutes,[5,7,8] treatment of ambulatory patients usually relies on orally administered drugs, which have a time course of action that does not closely match the experience of the pain. There is reason to believe that drug formulations with a rapid onset of effect may be more effective and, for this reason, there is growing interest in the development of drugs for BTP that have this characteristic.

This study establishes the efficacy, safety, and tolerability of FBT in the management of BTP in opioid-treated patients with cancer. Mean measures of the analgesic effect of FBT separated from placebo as early as 15 minutes after administration and the extent of separation increased up to and including the 60-minute time point. A $\geq 33\%$ reduction in PI, considered a clinically relevant effect,[23] occurred by 15 minutes in 13% of episodes treated with FBT; by 30 minutes, this level of response was observed in 48% of episodes. PI decreased from a mean of 6.9 at baseline to 4.6 at 30 minutes. Analgesic effects were not related to demographics or prior opioid regimen. Although patients with all types of pain responded, those with neuropathic pain responded better than those with nociceptive pain. This finding has uncertain significance and will require further investigation. At 60 minutes after administration, the majority of patients rated the global performance of FBT as at least "good."

Treatment-related AEs were largely limited to adverse effects typical of opioids (ie, dizziness, headache, nausea). Twelve (10%) and 3 (2%) of the 123 enrolled patients withdrew from the titration and double-blind periods, respectively, as a result of AEs. The use of titration from an initial low dose and the use of around-the-clock (ATC) and previous supplemental opioids presumably reduced the likelihood of intense adverse effects. Only 2 patients could not tolerate the drug as a result of its effects on the oral mucosa.

The crossover design of the double-blind period allowed the individual patient to serve as his or her own control, and consequently data from at least 1 episode of BTP treated with FBT and 1 episode in which placebo was administered must have been evaluable. Out of the 77 patients who entered the double-blind treatment period, 72 were evaluable for efficacy, including 4 who discontinued during the double-blind period. Six more patients who received all 10 doses had single interspersed missing values for $SPID_{30}$. It is unlikely that the missing values affected the overall results. We used the last-observation-carried-forward method to fill in both the trailing missing values of the 4 patients and the interspersed single missing values for the 6 patients. The F test for the treatment main effect for $SPID_{30}$ remained highly significant ($P < 0.0001$) although the effect size was slightly diminished, from 1.23 to 1.15.

Overall, 65% of patients were able to find an effective dose of FBT during the titration phase. There appeared to be no relationship between the effective dose of FBT and either the dose of the ATC opioid regimen or the supplemental opioid taken at the start of the study. A similar lack of relationship between the doses of an ATC opioid and OTFC, another transmucosally administered opioid, has been shown in several studies.[24–26] Therefore, titration, rather than dose selection based on a proportionate fraction of the ATC dose, is needed to establish an effective dose of FBT for individual patients. The reason for this lack of relationship between the effective dose of FBT and patients' scheduled or previous supplemental opioid doses is unknown. Although it is conventional practice to offer 5% to 15% of the total daily dose as the starting dose for BTP, this applies only to the use of oral medication and has not been evaluated in clinical studies of BTP for any opioid. Twenty of the 123 enrolled patients (16%) did not report satisfactory relief at the highest dose allowed during titration. Presumably, some of these patients would have been effectively treated with a higher dose. The proportion of patients who did identify an effective dose of FBT was only slightly lower than that observed during the titration phases of the OTFC studies, which explored doses as high as 1600 μg.[24,27,28] Further studies will be needed to determine the relative potency of FBT versus OTFC, and should FBT be shown to be substantially more potent, additional analysis of pharmacokinetic-pharmacodynamic relationships will be needed to evaluate the extent to which this difference is attributable to more extensive drug absorption.

Additional studies are also needed to compare the clinical effectiveness of rapid-onset opioids like FBT and the short-acting oral opioids now most commonly used for the treatment of BTP. A study of OTFC suggested that this formulation is better than oral morphine for the treatment of BTP, but the methodology used in this study could not provide definitive answers to questions about the comparability of formulations or the specific characteristics that may distinguish them in the clinical setting.[16]

This study provides the first evidence that FBT provides rapid-onset analgesia and is effective and safe as a treatment for cancer-related BTP. Further studies of this formulation are warranted.

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EXHIBIT 5

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Fentanyl buccal soluble film (FBSF) for breakthrough pain in patients with cancer: a randomized, double-blind, placebo-controlled study

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Background: Fentanyl buccal soluble film (FBSF) has been developed as a treatment of breakthrough pain in opioid-tolerant patients with cancer. The objective of this study was to evaluate the efficacy of FBSF at doses of 200–1200 μg in the management of breakthrough pain in patients with cancer receiving ongoing opioid therapy.

Patients and methods: This was a multicenter, randomized, double-blind, placebo-controlled, multiple-crossover study that included opioid-tolerant adult patients with chronic cancer pain who experienced one to four daily episodes of breakthrough pain. The primary efficacy assessment was the sum of pain intensity differences at 30 min (SPID30) postdose.

Results: The intent-to-treat population consisted of 80 patients with ≥1 post-baseline efficacy assessment. The least-squares mean (LSM ± SEM) of the SPID30 was significantly greater for FBSF-treated episodes of breakthrough pain than for placebo-treated episodes (47.9 ± 3.9 versus 38.1 ± 4.3; $P = 0.004$). There was statistical separation from placebo starting at 15 min up through 60 min (last time point assessed). There were no unexpected adverse events (AEs) or clinically significant safety findings.

Conclusions: FBSF is an effective option for control of breakthrough pain in patients receiving ongoing opioid therapy. In this study, FBSF was well tolerated in the oral cavity, with no reports of treatment-related oral AEs.

Key words: breakthrough cancer pain, clinical study, fentanyl buccal soluble film

introduction

Pain related to chronic conditions such as cancer is often characterized by two components. The first component is persistent pain, and the recommended treatment is long-acting opioid products. The second component is often referred to as 'breakthrough pain'. Breakthrough pain is defined as the 'transient exacerbation of pain occurring in a patient with otherwise controlled persistent pain' [1]. An international survey of 58 clinicians in 24 countries evaluated a total of 1095 patients with cancer pain of an intensity that needed treatment with opioid analgesics to determine the prevalence of breakthrough pain [2]. Breakthrough pain was reported in 64.8% of these patients and was associated with higher pain scores and functional impairment on the Brief Pain Inventory [2].

Breakthrough pain episodes have been routinely treated with oral short-acting opioids, including hydrocodone, hydromorphone, morphine, and oxycodone [3]. Although these treatments are widely used, the variable absorption of oral opioids from the gastrointestinal tract may result in delayed pain relief (PR) (up to 40 min after administration) [4] and may lead to variability in the therapeutic effect. In a Pan-European survey [5], it was reported that 63% of patients with cancer receiving prescription analgesics reported breakthrough pain or inadequate PR. Of those patients, 58% reported that they had inadequate PR at all times.

As an alternative to oral administration, transdermal and transmucosal routes of administration have been used to deliver pain medication. With transmucosal delivery, absorption through the oral mucosa from either the buccal cavity or sublingually is more rapid than oral absorption [6]. Other benefits of oral transmucosal delivery include minimization of first-pass metabolism and better tolerance for patients with dysphagia (especially dysphagia due to conditions such as head and neck cancer [7]) or those who have experienced nausea or vomiting [8].

Fentanyl is a potent opioid analgesic that is well absorbed via the oral mucosa. Currently, there are various formulations approved by regulatory authorities. Oral transmucosal fentanyl citrate (OTFC) (United States and Europe: Actiq®; Cephalon, Inc., Frazer, PA) is a buccal formulation composed of a fentanyl lozenge on a stick. This formulation requires patient effort for administration, and absorption is dependent on the individual application technique. A second buccal formulation, the

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fentanyl buccal tablet (FBT) (United States: Fentora®; Europe: Effentora®; Cephalon), has been approved in the United States and Europe. This formulation utilizes an effervescence reaction that is postulated to be responsible of an enhanced fentanyl absorption through the buccal mucosa above that achievable with OTFC. More recently, a sublingual tablet formulation of fentanyl (Europe: Abstral®; Orexo, Inc., Uppsala, Sweden) that uses mucoadhesives to hold the fentanyl in contact with the mucosa membrane has been marketed in Europe.

The most recent product to be approved by the United States Food and Drug Administration, a fentanyl buccal soluble film (FBSF) (United States: Onsolis®; Meda Pharmaceuticals Inc., Somerset, NJ; Europe: Breakyl® and Buquel®), has been developed to control breakthrough pain in patients with cancer and is intended for direct application to the oral mucosa. FBSF utilizes BioErodible MucoAdhesive (BEMA™; BioDelivery Sciences, Inc., Raleigh, NC) technology to deliver fentanyl across the buccal mucosa. The technology uses a dual-layer polymer film consisting of a mucoadhesive layer that contains the active drug and an inactive layer that helps to prevent diffusion of drug into the oral cavity. The mucoadhesive layer adheres to a moist mucosal membrane in seconds. FBSF starts to dissolve in minutes and is completely dissolved within 15–30 min after application without patient effort, requiring only a minimal amount of saliva to dissolve once adhered. Previous studies have shown that when delivered by this system, the proportion of the fentanyl dose that undergoes transmucosal absorption is ~50% and the absolute bioavailability is ~71%. The direct relationship between the surface area of the dose unit and the dose of fentanyl combined with the mucosa contact time results in consistent plasma concentrations when equivalent doses are delivered by single or multiple dosage units [9].

The objective of the present study was to evaluate the efficacy and safety of FBSF at doses ranging from 200 to 1200 μg in the management of breakthrough pain in patients with cancer receiving around the clock opioid therapy.

methods

trial design

This was a multicenter, randomized, double-blind, placebo-controlled, crossover study comparing FBSF with placebo for the treatment of breakthrough pain in patients with cancer receiving a stable opioid regimen for persistent pain. Breakthrough pain was defined as moderate-to-severe pain that occurred at a specific site for a transitory period against a background of persistent pain controlled by the around the clock opioid regimen. The study consisted of a screening period of up to 1 week, an open-label titration period of up to 2 weeks, a double-blind period of up to 2 weeks, and a 1-day follow-up. In the titration period, patients were issued an electronic diary and a dose-titration kit containing five doses of each of the five dose strengths (200, 400, 600, 800, and 1200 μg) of FBSF. Each subject started with the 200-μg dose and increased their dose in a stepwise manner until adequate PR was achieved. Patients unable to identify a dose that produced satisfactory PR and those not completing the titration within 2 weeks were discontinued from the study. Patients who identified a dose that produced satisfactory PR for at least two target breakthrough pain episodes were eligible to enter the double-blind crossover period. During the double-blind period, patients received nine doses of study medication: six contained fentanyl at the effective dose for that patient and three were placebo. The order in which the patient received FBSF or placebo was determined by a computer-generated randomization code. At no time did patients receive two placebos in a row. Subjects were allowed to use their usual rescue medication if adequate PR was not realized within 30 min. Patients were not allowed to take another study dose for 4 h after their last dose of study drug. Any subsequent dose of study medication was for the emergence of a new target breakthrough pain episode and not an unresolved previously treated episode. Subjects remained in the double-blind period of the study until all nine doses of study medication were taken or until 14 days after entry into the double-blind period of the study.

The study protocol was approved by the institutional review board of each participating center. The study was conducted in accord with provisions of the World Medical Association Declaration of Helsinki and its most recent amendment concerning medical research in humans (2004) and conformed to all local laws and regulations (whichever provided the greater protection to individual patients). Documentation and procedures complied with the International Conference on Harmonisation Guideline E6 (R1) and the USA Code of Federal Regulations (Title 21, Part 50). All patients read and signed an approved informed consent form before enrollment procedures commenced.

patients

inclusion criteria. Patients eligible for the study were men or nonpregnant nonlactating women aged 18 years or older with pain associated with cancer or cancer treatment that required opioid therapy. The opioid dosage regimen must have been stable at the time of enrollment and was required to be equivalent to 60–1000 mg/day of oral morphine or 50–300 μg/h of transdermal fentanyl. Eligible patients were experiencing one to four episodes of breakthrough pain daily that required opioids for pain control, for which opioids provided at least partial relief.

exclusion criteria. Patients with more than four episodes of breakthrough pain per day and those with rapidly escalating pain that the investigator believed may require an increase in the dosage of the background opioid were not eligible for the study, as were those who had received strontium 89 during the previous 6 months and those receiving any other therapy that could alter pain or the patient's response to pain medication.

drug administration

Eligible patients received instruction on handling and application of FBSF dose units. Patients were instructed to apply the mucoadhesive side of the thin film unit (about half the thickness of a business card or roughly equivalent to 2.5 dollar bills) to a moistened (saliva or water) buccal mucosa and to hold it in place for 5 s. The FBSF dose unit adheres to the mucosal membrane, becoming pliable within a minute, and then completely dissolves over a period of ~15–30 min.

Patients were allowed to use their usual rescue medication 30 min after self-administration of a study dose for episodes of pain that were not adequately controlled by the study medication.

assessments

efficacy. Pain intensity (PI) and PR were assessed at 5, 10, 15, 30, 45, and 60 min after each double-blind study dose. PI was measured on an 11-point scale (0 = no pain and 10 = worst pain) and the PI difference calculated as the baseline PI minus the assessment point PI. PR was measured on a 5-point scale (0 = no relief to 4 = complete relief). PI differences (PID = baseline PI minus PI at assessment point) were calculated, and the weighted sum over the first 30 min postdose (SPID30) was defined as the primary outcome measure. Secondary outcome measures included PID and PR calculated at various time points throughout the study period and the sums of PID (SPID) were calculated over various intervals. Global satisfaction was assessed on a 5-point scale (poor, fair, good, very good, and excellent) at the time of rescue or 60 min after study dose.

safety. A complete medical history, including cancer diagnosis, recent therapeutic decisions, and drug history, was assessed at the screening visit. A complete physical examination was carried out and vital signs measured at the screening and follow-up visits. Adverse events (AEs) were reported and assessed throughout the study with an electronic diary. Concomitant medications were monitored throughout the study.

statistical analyses

Efficacy analyses were conducted using the intent-to-treat (ITT) population, defined as all patients who entered the double-blind phase of the trial, who took at least one dose of study medication and had at least one pain assessment within the 30-min postdose period. The safety population was defined as all patients who received at least one dose of study medication in the dose-titration and double-blind treatment phases of the study.

All statistical analyses were carried out by using a two-sided hypothesis test with a type I error (alpha) of 0.05 (i.e., a 5% level of statistical significance). Efficacy data are presented as least-squares means (LSM) and standard errors. The primary efficacy parameter, SPID30, was analyzed using a mixed model of repeated measures with fixed effects for treatment, pooled site, and a random effect for subjects. The secondary efficacy parameters were analyzed using the one-sample Wilcoxon signed rank test.

results

patient disposition and demographics

The study was conducted at 30 clinical sites in the United States between 24 February 2006 and 14 March 2007. A total of 152 patients were screened and enrolled in the study, and 151 patients received at least one dose of study medication and were included in the safety population (Figure 1).

Of the 151 patients enrolled in the titration phase, 69 (45.7%) discontinued the study. The reasons for withdrawal were the following: 17 (11.3%) for AEs, 15 (9.9%) because of difficulties or noncompliance with the electronic diary, 14 (9.3%) withdrew consent without explanation, 8 (5.3%) were withdrawn for protocol violations, 7 (4.6%) because they had less than a single episode of breakthrough pain a day, 5 (3.3%) for lack of efficacy, and 3 (2.0%) patients for administrative reasons.

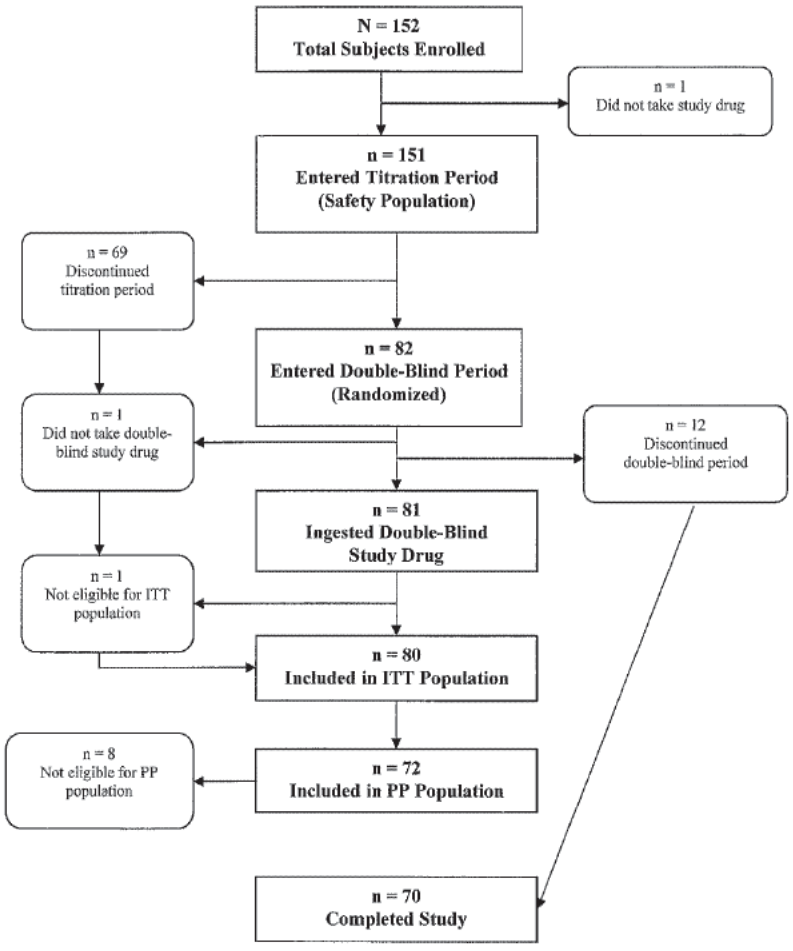

Figure 1. Flow of patients through the study. ITT, intent-to-treat; PP, per protocol.

Twelve patients (7.9%) discontinued prematurely from the double-blind phase of the study for the following reasons: 4 (4.9%) withdrew consent, 3 (3.7%) because of AEs, 2 (2.4%) for noncompliance with the electronic diary, 2 (2.4%) for not consistently treating one episode of pain per day, and 1 (1.2%) for lack of efficacy.

A total of 70 patients in the safety population did not receive any study drug in the double-blind treatment phase of the study, and 1 patient did not have a pain assessment within 30 min of taking a dose of study drug during the double-blind phase of the study; thus, the ITT population consisted of 80 patients.

A summary of the demographic characteristics of patients included in the safety and efficacy populations is provided in Table 1. There were no important differences in the baseline characteristics of the safety and ITT populations. Breast cancer (23%), lung cancer (17%), colorectal cancer (11%), gastroesophageal cancer (7%), pancreatic cancer (6%), and head and neck cancer (5%) were the most common cancer types in the safety population. Overall, patients had suffered from the current primary cancer for a mean period of 3.2 years with a median of 1.6 years and a range of <1 to >30 years. More than half of the patients (55.6%) had received chemotherapy and one-quarter (25.2%) had received radiation therapy in the last 6 months before study entry.

For approximately half of the patients in the safety population, the pain pathophysiology for both persistent pain and target breakthrough pain was somatic and/or visceral. Forty-nine patients (32.5%) also experienced neuropathic pain. For most patients in the safety population, the pain syndrome for persistent and target breakthrough pain was typically related to direct tumor involvement (84.8% and 86.1% of patients, respectively) or due to somatic/visceral lesions (83.4% and 84.8% of patients, respectively).

The most common stable opioid regimen was transdermal fentanyl for persistent pain, taken by 46.4% of patients, and hydrocodone for target breakthrough pain, taken by 42.4% of patients. Long-acting oral morphine was used in 23.8% of patients for persistent pain and short-acting oral morphine was used in 26.5% of patients for target breakthrough pain. For nearly all patients [149 of 151 (98.7%)] in the safety population, there were minimal opioid side-effects from the current daily opioid dose.

Table 1. Demographic data

Demographic	Safety population ($n = 151$)	Efficacy (ITT) population ($n = 80$)
Gender, *n* (%)		
Male	66 (44)	36 (45)
Female	85 (56)	44 (55)
Mean (SD) age in years	57.1 (12.2)	56.8 (13.0)
Age in years, *n* (%)		
<65	104 (69)	55 (69)
≥65	47 (31)	25 (31)
Race, *n* (%)		
White	131 (86.8)	72 (90.0)
Black	12 (7.9)	6 (7.5)
Asian	1 (0.7)	0
Other	7 (4.6)	2 (2.5)
Mean (SD) height, cm	168.7 (9.8)	169.2 (9.3)
Mean (SD) weight, kg	73.0 (19.1)	74.5 (17.8)
Mean (SD) duration since diagnosis in years	3.2 (4.5)	3.7 (5.2)
Median (range) duration since diagnosis in years	1.6 (0.0–30.3)	2.17 (0.0–30.3)
Cancer treatment in previous 6 months, *n* (%)		
Chemotherapy	84 (56)	43 (54)
Radiation	38 (25)	15 (19)

ITT, intent-to-treat; SD, standard deviation.

dosing

Patients received a mean of 9.3 doses of FBSF during the dose-titration phase. During the double-blind treatment phase, patients received a mean of 5.5 doses of FBSF and 2.8 doses of placebo. Patients received a total of 14.0 doses of FBSF over the course of the study.

In the double-blind portion of the study, the number of individuals dosed at 200, 400, 600, 800, or 1200 μg was 4 (4.9%), 15 (18.5%), 23 (28.4%), 19 (23.5%), and 20 (24.7%), respectively. The effective dose for most patients was ≥400 μg. The mean duration of exposure to the study drug was 6.6 days in the titration period, 5.9 days in the double-blind period, and 10.1 days in the entire study period. The minimum period of exposure was 1 day and the maximum was 27 days.

efficacy

At baseline, the mean PI score was 6.9 and the median PI score was 7.0 for both FBSF- and placebo-treated episodes. A total of 394 FBSF episodes and 197 placebo episodes were included in the ITT analysis of the primary efficacy end point.

The LSM ± SEM of the SPID30, the primary efficacy variable, was significantly greater for FBSF-treated episodes of breakthrough pain than for placebo-treated episodes (47.9 ± 3.9 versus 38.1 ± 4.3; $P = 0.004$). The SPID values for FBSF-treated episodes were consistently greater compared with placebo-treated episodes at all postdose time points. There was statistically significant separation from placebo starting at 15 min postdose ($P < 0.05$) through 60 min postdose [the last time point assessed ($P < 0.001$)] (Figure 2).

Similarly, PID (Figure 3) values for FBSF-treated episodes were consistently greater compared with placebo-treated episodes at 10 min postdose and all time points beyond, with the difference reaching statistical significance at 30 min. The PR values were statistically significant from placebo starting at 30 min postdose ($P < 0.01$) and continuing until the last assessment ($P < 0.01$).

The percentage of episodes with a 33% or 50% decrease in pain was also significantly greater with FBSF than with placebo (Table 2). Overall satisfaction with the study drug was significantly greater with FBSF than with placebo (mean score 2.0 versus 1.5, respectively; $P < 0.001$). Moreover, more patients rated their overall satisfaction with FBSF as good, very good, or excellent compared with placebo (Figure 4). Conversely, fewer patients rated their overall satisfaction with FBSF as poor or fair

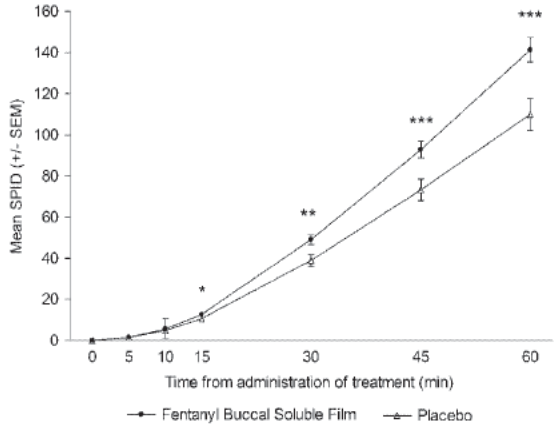

Figure 2. Mean sum of pain intensity difference (SPID) scores over time.*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. SEM, standard error of the mean.

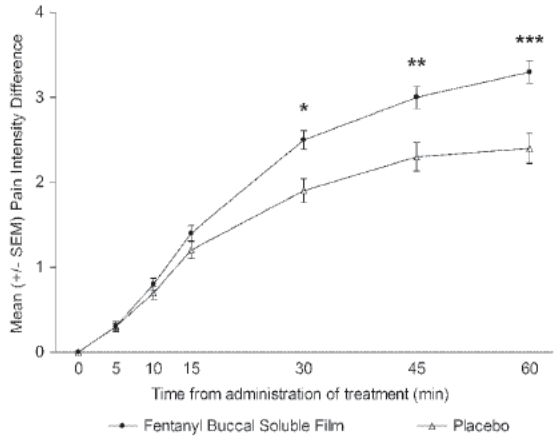

Figure 3. Mean pain intensity difference over time.*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. SEM, standard error of the mean.

compared with placebo (Figure 4). The mean (± SEM) number of episodes when rescue medication was used was significantly lower after treatment with FBSF than with placebo (30.0% ± 3.5% versus 44.6% ± 4.4%; $P = 0.002$).

safety

Twenty-three patients (15.2%) experienced 29 serious AEs. None of these serious AEs were considered to be related to the study drug. Respiratory depression was not reported by any patient enrolled in the study. There were four deaths during the study, none of which were considered to be study drug related.

Twenty-one patients (13.9%) discontinued study drug administration because of treatment-emergent AEs, including 9 serious AEs and 12 nonserious AEs. Nausea and vomiting were the most common AEs leading to permanent study drug discontinuation (3.3% of patients, respectively).

Treatment-emergent AEs were reported by 75 patients (49.7% of 151 patients) during the titration period and 34 patients (42% of 81 patients) during the double-blind period. The most common treatment-emergent AEs were typical of opioid administration and occurred with similar frequency during the titration and double-blind phases. Treatment-emergent AEs reported during the titration phase included nausea (9.3%), vomiting (9.3%), somnolence (6.0%), dizziness (4.6%), and headache (4.0%). Treatment-emergent AEs reported during the double-blind phase included nausea (9.9%), vomiting (9.9%), and headache (1.2%).

Most AEs [213 of 273 (78.0%)] in 47 patients were not considered to be drug related. A total of 56 drug-related AEs were reported by 37 of the 151 patients (24.5%) included in the safety population. One patient had four AEs, and it could not be determined whether those events were drug related. The most common drug-related AEs were gastrointestinal disorders and central nervous system disorders (Table 3). These AEs included somnolence (6.0%), nausea (5.3%), dizziness (4.6%), and vomiting (4.0%). These AEs are commonly associated with opioid therapy.

Only five patients (3.3%) reported oral AEs ($n = 2$, mild mucosal inflammation; $n = 3$, oral candidiasis) and all these events were considered to be unrelated to study treatment in the opinion of the investigator. No oral ulcerations, pain, or edema associated with the study drug were observed in the study population.

discussion

The results of this study demonstrate that FBSF is more effective than placebo for the management of breakthrough pain in opioid-tolerant patients with cancer. The SPID values were significantly greater for FBSF-treated episodes than for placebo-treated episodes beginning 15 min after drug administration and continuing through 60 min. Similarly, pain scores for FBSF-treated episodes were significantly lower than for placebo-treated episodes at 30, 45, and 60 min after dosing. At 30 min postdose, reductions in PI of at least 33% and of at least 50% were obtained in significantly more FBSF-treated episodes than in placebo-treated episodes ($P = 0.009$ and $P = 0.002$, respectively). Patients gave favorable ratings to a numerically higher proportion of pain episodes treated with FBSF than with placebo ($P < 0.001$).

Of 152 patients on stable opioid therapy for cancer pain who entered the dose-titration phase of the study, 53.9% entered the double-blind phase. The most common reasons for dropout from the titration phase were noncompliance with study procedures, including use of the electronic diary card. Of the subjects who began titration, 3.3% did not continue in the study because they were not able to find an effective dose of FBSF for breakthrough pain.

It has been reported that more than half of patients receiving prescription medicine for cancer pain experience inadequate PR or breakthrough pain [5]. This finding indicates that additional pharmacotherapeutics that are well tolerated and have rapid onsets of action are needed to treat this patient population. Transmucosal fentanyl preparations are approved in the United States for the treatment of breakthrough pain in patients with cancer, including OTFC, FBT [10, 11], and FBSF. OTFC has been shown to provide more effective PR than immediate-release morphine in a study population similar to

Table 2. Percentage of episodes with decreases in pain scores (mean ± SEM)

Parameter	Treatment	Time post administration (min)			
		15	30	45	60
Percentage of episodes with ≥33% reduction in pain scores	FBSF	26.4 (3.55)	47.3 (4.05)	57.5 (3.93)	64.3 (3.72)
	Placebo	21.3 (3.66)	38.2 (4.45)	46.5 (4.50)	48.2 (4.51)
	P value	0.100	0.009	0.004	<0.001
Percentage of episodes with ≥50% reduction in pain scores	FBSF	14.9 (2.81)	32.8 (3.78)	41.1 (4.11)	46.3 (4.17)
	Placebo	14.7 (3.35)	24.1 (3.87)	30.5 (4.10)	34.0 (4.30)
	P value	0.963	0.002	0.008	0.005

FBSF, fentanyl buccal soluble film.

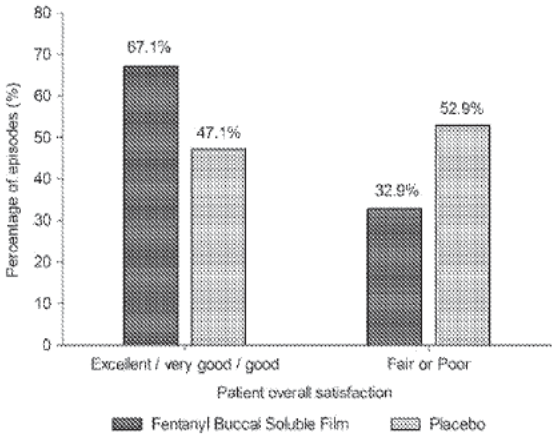

Figure 4. Overall satisfaction with study drug.

Table 3. Incidence of drug-related adverse events that occurred in two or more patients (n = 151)

Adverse event	Incidence, n (%)
Somnolence	9 (6.0)
Nausea	8 (5.3)
Dizziness	7 (4.6)
Vomiting	6 (4.0)
Headache	4 (2.6)
Constipation	3 (2.0)
Dry mouth	2 (1.3)
Dysgeusia	2 (1.3)
Pruritus	2 (1.3)
Confusional state	2 (1.3)

the group described in the current study [12]. FBSF has been shown to produce plasma fentanyl concentrations earlier and greater than an equal dose of OTFC in normal volunteers [13].

FBSF was safe and well tolerated by patients enrolled in this study. The AEs reported during the study were typical of those associated with opioid analgesics. No patients experienced respiratory depression and none of the serious AEs were considered to be study drug related. No drug-related oral AEs were reported in this study. The dropout rate observed in this study due to treatment-emergent AEs was 13.9%. Five patients (3.3%) withdrew due to lack of efficacy during the open-label titration phase and one patient (1.2%) withdrew due to lack of efficacy during the double-blind phase. No patients dropped out due to site administration AEs.

There are several important clinical implications of the results reported here. There was a statistically significant decrease in SPID compared with placebo as early as 15 min after drug administration and continuing through 60 min; thus, FBSF provides rapid effective relief of breakthrough pain in patients with cancer. FBSF is safe and well tolerated, with no oral AEs attributed to the drug. There was a low rate of failure to control pain in these patients. These findings are of particular importance considering the special needs of patients with cancer who may have trouble swallowing, mucosal problems (mucositis and thrush), or xerostomia.

One interesting aspect of this study was the unusual placebo response to the film. When the results of the study of FBT by Portenoy et al. [14] are compared with that in the FBSF study, it is apparent that the response to placebo was consistently higher in our trial [e.g., placebo PID at 30 min was 36% higher in this trial than in the buccal tablet trial (1.9 versus 1.4)]. The reason for the higher placebo response in a similar patient population is not readily apparent, but there are several possibilities. Placebo rates tend to be high in pain studies, with estimates ranging from 15% to 53% [15], and expectation plays an important role in their magnitude [16–18]. In this sense, the innovative and unconventional technology of FBSF might have generated high expectations in both investigators and patients and contributed to the high placebo response rate. Specifically, the bilayer delivery technology used for FBSF incorporates the fentanyl into the layer that adheres to the buccal mucosa and isolates the fentanyl from the saliva by the inactive layer that contains the taste masking agents. It is believed that this design not only optimizes fentanyl delivery across the buccal mucosa but also minimizes fentanyl contact with the taste buds, making it very difficult for most patients to distinguish between active and placebo treatments based on taste.

This study has the limitation of being done in an enriched population of patients, those who responded during the open-label titration phase of the study. Thus, our results may not apply to all patients seen in clinical practice. However, there was a low rate of failure to control pain in patients who continued into the double-blind phase of the study.

In conclusion, FBSF is an effective option for control of breakthrough pain in patients receiving ongoing opioid therapy. In this study, FBSF was well tolerated and there were no reports of treatment-related AEs.

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disclosure

LNG and IT are employees of Meda Pharmaceuticals. ALF is an employee and shareholder of BioDelivery Sciences International, the developer of FBSF.

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EXHIBIT 7

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A multicenter, placebo-controlled, double-blind, multiple-crossover study of Fentanyl Pectin Nasal Spray (FPNS) in the treatment of breakthrough cancer pain

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ABSTRACT

This randomized, double-blind, crossover study assessed the efficacy and tolerability of a new rapid onset nasal fentanyl formulation (Fentanyl Pectin Nasal Spray; FPNS) for breakthrough cancer pain (BTCP). Eighty-three of 114 patients experiencing one to four BTCP episodes/day while taking ⩾60 mg/day of oral morphine or equivalent successfully identified an effective dose of FPNS during a titration phase and entered a double-blind phase in which 10 BTCP episodes were treated with this effective dose (7) or placebo (3). Compared with placebo, FPNS significantly improved mean summed pain intensity difference (SPID) from 10 min ($P < 0.05$) until 60 min ($P < 0.0001$), including the primary endpoint at 30 min ($P < 0.0001$). FPNS significantly improved pain intensity (PI) scores as early as 5 min ($P < 0.05$); pain intensity difference (PID) from 10 min ($P < 0.01$); and pain relief (PR) scores from 10 min ($P < 0.001$). More patients showed a clinically meaningful (⩾2-point reduction in PI) pain reduction from 10 min onward ($P \leqslant 0.01$) and 90.6% of the FPNS-treated versus 80.0% of placebo-treated BTCP episodes did not require rescue medication ($P < 0.001$). Approximately 70% of patients were satisfied or very satisfied with the convenience and ease of use of FPNS. Only 5.3% of patients withdrew from treatment due to adverse events, no significant nasal effects were reported, and 87% of patients elected to continue open-label treatment post-study. In this short-term study, FPNS was safe, well tolerated, and rapidly efficacious for BTCP.

1. Introduction

Breakthrough pain, defined as a transitory exacerbation of pain that occurs on a background of otherwise controlled persistent pain [16], has been reported to occur in 33–95% of populations with cancer pain [19,20,26]. Typically, patients with chronic cancer pain experience three to four breakthrough cancer pain (BTCP) episodes daily, and the typical BTCP peaks within minutes and persists for a short period (typically less than 45 min) [19–21]. Patients with BTCP are more likely to have severe pain, psychological distress, impaired function, and poorer quality of life [2,21]. BTCP also has been associated with higher health care costs [10].

Historically, BTCP has been managed with doses of short-acting oral opioid drugs, offered "as needed" to supplement a fixed-schedule opioid regimen [1,16]. Although such treatment with a "rescue dose" is commonplace, its known pharmacodynamic relationship does not closely match the typical time course of a BTCP episode. For example, the onset of effect of oral short-acting formulations of morphine or oxycodone usually begins at least 20 min after the dose and the peak effect does not occur for nearly an hour [1,4]. This recognized mismatch between oral drug pharmacodynamics and the time course of a typical BTCP episode has led to efforts to identify alternative drugs and delivery systems to improve pain control.

New fentanyl delivery systems for BTCP have focused on the transmucosal route of administration, which is capable of yielding pharmacokinetic profile characterized by a high early fentanyl concentration and enhanced early systemic fentanyl exposure [6,27]. Various transmucosal routes have been studied, including buccal, sublingual, and intranasal. Among these, the intranasal route may yield particularly rapid absorption owing to the high vascularity and permeability of nasal tissues [5,12]. Rapid absorption is supported by pharmacokinetic measurements demonstrating a short arterial T_{max} and a significant arteriovenous difference in fentanyl concentration after intranasal administration [17]. The

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pharmacokinetic inconsistencies related to swallowing part of a dose, which could lead to dose-to-dose variability in effects during repeated oral transmucosal administration, also might be limited with intranasal drug delivery [12]. This potential advantage may be enhanced by new technologies that modulate drug release and reduce the risk of nasal drip or unintentional swallowing [30].

Fentanyl Pectin Nasal Spray (FPNS) uses a proprietary pectin-based transmucosal delivery system (PecSys™) to modulate drug release. FPNS is delivered as a low-volume fine mist of uniform droplets that form a gel on contact with the calcium ions present in the mucosal membrane secretions. Compared with oral transmucosal fentanyl citrate, the pharmacokinetics of FPNS are characterized by reduced time to peak plasma values and significantly increased bioavailability [30].

The primary objective of this study was to demonstrate the efficacy of FPNS in the treatment of BTCP in patients who are receiving regular opioid therapy. Secondary objectives were to demonstrate FPNS onset of action, time to clinically meaningful pain relief, safety, tolerability, and acceptability.

2. Methods

2.1. Study design

This multicenter, randomized, placebo-controlled, double-blind, multiple-crossover study was conducted at 36 centers in the United States, Costa Rica, and Argentina. The study protocol was executed in accordance with regulatory requirements and good practice guidelines, and was approved by institutional review boards at the participating institutions. All participating patients provided signed informed consent. The maximum study duration for individual patients was set at 8 weeks.

2.2. Patients

Adult men or women were eligible 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 oral morphine per day for background pain, and had one to four episodes of moderate to severe BTCP per day. If a patient had more than one type of BTCP or had breakthrough pain in more than one location, only one of the pains was identified as a "target" BTCP.

Patients who had uncontrolled or rapidly escalating background pain and those who were medically unstable were not eligible for the study. Other exclusion criteria included breakthrough pain not primarily related to cancer, past inability to tolerate fentanyl or other opioids, history of alcohol or substance abuse, treatment with monoamine oxidase inhibitors, and treatment with radiotherapy or other investigational drug within the previous 30 days. The concomitant use of other medications or interventions that might have impacted the patient's experience of pain between and during episodes (such as analgesic or antiepileptic medication, radiotherapy, or chemotherapy) was to be avoided during the double-blind period or, in case of medications of these types, the dose had to have been stable for between 2 and 3 weeks and was to remain stable during the study. Treatment with specific medications with a known potential for hazardous interaction with fentanyl (such as monoamine oxidase inhibitors) was also excluded. Additionally, patients with any disorder or medication use likely to adversely affect the normal functioning of the nasal mucosa were not eligible.

2.3. Procedures

Consenting patients who met inclusion and exclusion criteria were allowed to enter an open-label titration phase, the objective of which was to treat a series of BTCP episodes with successively higher doses of FPNS until either an effective dose was found, drop-out occurred due to adverse events (AEs), or the drug was demonstrated to be ineffective at the highest dose tested. A dose was considered "effective" if two episodes of target BTCP were successfully treated (defined as acceptable pain relief [PR] without unacceptable adverse effects) with the same dose of FPNS. If PR was unacceptable 30 min after taking FPNS, the patient could use his or her usual rescue medication.

During this open-label phase, FPNS doses were titrated from an initial dose of 100 μg. Doses were sequentially escalated to 200 μg, 400 μg, and then 800 μg, if necessary, to identify the effective dose. If the 800 μg dose was ineffective, the patient was discontinued from the study.

Only patients who identified an effective dose were eligible to continue into the double-blind phase. The objective of this phase was to treat a total of 10 BTCP episodes with either the effective dose of FPNS (seven episodes) or an identically appearing placebo (three episodes).

During the double-blind phase, patients received 10 separate "blinded" bottles, each of which contained either FPNS at the effective dose or placebo, identified only by a number, 1–10, by random assignment. Patients were instructed to use the bottles in the order designated, which was established by a computer-generated schedule of active drug and placebo in a 7:3 ratio. The patient and all personnel involved with the study (including investigators and investigation site personnel) were blinded to the medication codes. The randomization code for each study site was kept in a sealed envelope (one per drug pack), to be opened only in a medical emergency.

Patients were instructed to treat no more than four BTCP episodes per day and to have an interval of at least 4 h between doses. Each episode was treated with a single dose. Pain that continued to require treatment 30 min after the dose of study medication could be treated with the patient's usual rescue medication. Patients also were instructed that an interval of at least 4 h was to elapse between the use of rescue medication and the next dose of FPNS. No protocol violations were identified by use of the e-diary. Any occurrence of acute pain other than the target BTCP could be treated using the patient's usual rescue drug.

2.4. Efficacy outcome measures

Electronic diaries (e-diaries) were used to collect patient data during the dose-titration and double-blind phases. Baseline pain intensity (PI) prior to treating a BTCP episode was recorded using an 11-point numeric scale (0 = no pain to 10 = worst possible pain). After this baseline measurement, the study drug was taken. The e-diary then provided cues so that both PI and PR scores were recorded at 5, 10, 15, 30, 45, and 60 min. PR was measured on a 5-point numeric scale (0 = none to 4 = complete). Use of rescue medications was recorded throughout the study.

During the double-blind phase, patients also were asked to rate overall satisfaction with the nasal spray at 30 and 60 min after each treated BTCP episode. The rating was obtained using a 4-point scale (1 = not satisfied to 4 = very satisfied). Similarly, at the end of the study (after the last treated BTCP episode), patients also rated the ease of use and convenience of the nasal spray on separate 4-point scales.

2.5. Safety and tolerability assessments

AEs were recorded throughout the study. Objective visual nasal assessments were performed by the study physician at screening and at the end of treatment. Subjective nasal assessments were performed by the patient using a 10-item questionnaire (each item

rated on a 4-point scale: 0 = absent to 3 = severe) before the first use of study drug, 1 h 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, burning/discomfort, bleeding of nose, cough, postnasal drip, sore throat, and taste disturbance.

2.6. Statistical analysis

The primary endpoint was the patient-averaged summed pain intensity difference 30 min after dosing (SPID30), defined as the cumulative sum of the recorded difference between PI and baseline at each time point from 5 to 30 min post dose. This endpoint was chosen because of the likelihood that it would best reflect the efficacy of the dose; at 30 min, it would be expected that the full dose would be absorbed, though the underlying pain related to the breakthrough episode would still be present for most patients. Approximately 80 patients were required for the double-blind phase of the study to detect a mean ± SD treatment difference of 2.25 ± 4.35 between FPNS and placebo in SPID30, with a 90% power and a significance level of 0.05.

Secondary endpoints included SPID at 10, 15, 45, and 60 min; PI scores at 5, 10, 15, 30, 45, and 60 min; and the pain intensity difference (PID) between scores at specific time points (5, 10, 15, 30, 45, and 60 min) and the baseline score. Onset of analgesia was analyzed by assessing the time when a $\geqslant$1-point reduction in PI was recorded. Other secondary endpoints included the PR scores at 5, 10, 15, 30, 45, and 60 min; total pain relief (TOTPAR) calculated as the cumulative sum of the recorded PR scores at 10, 15, 30, 45, and 60 min, respectively; the percentage of episodes of BTCP that required additional rescue medication within 60 min, and the extent to which each treated episode was followed by clinically meaningful pain relief (defined as a $\geqslant$2-point reduction in PI [9]) after FPNS versus placebo therapy. A $\geqslant$2-point reduction in SPID also was evaluated in these analyses.

The statistical analysis used a modified intent-to-treat (ITT) approach, which included all patients in the randomized population who treated at least one pain episode with FPNS and one pain episode with placebo, and, for these episodes, had at least a baseline and one post-baseline PI measurement. The safety analysis set included all patients who received at least one dose of FPNS. Analyses were performed at (1) the patient-level (patient averages, percentage of patients) and (2) at the episode-level (percentage of episodes) as an indicator of the consistency of effect. The last-observation-carried-forward (LOCF) method was used to input missing data prior to calculating the average values for each patient. The mean value of each variable for each patient was determined (up to seven target BTCP episodes per patient treated with FPNS and up to three target BTCP episodes per patients treated with placebo), giving two numbers – the mean score for episodes treated with FPNS and the mean score for episodes treated with placebo – per variable, per patient.

For the primary endpoint, analysis of covariance (ANCOVA) was used to compare treatments, with the SPID30 score as the dependent variable and both treatment (FPNS or placebo) and pooled study center included as covariates. Secondary endpoints comparing treatment differences in PI, PID, SPID, PR, and TOTPAR at each time point were analyzed using a model similar to the primary endpoint. In addition, the number and percentage of (a) patients and (b) episodes in each treatment group achieving PI scores $\geqslant$1 and $\geqslant$2 and SPID scores $\geqslant$2 were summarized. Tests for association between endpoint and treatment were performed using the McNemar test for correlated 2 × 2 binomial endpoints for the patient-level analysis and a multilevel model for binary data with random effects for the episode-level analysis.

For the ease-of-use and convenience assessments performed after the last treated episode, patient-averaged scores by treatment were categorized as neither satisfied nor dissatisfied (score <3) and satisfied or very satisfied (score $\geqslant$3). Safety data during the titration and double-blind phases were summarized by treatment.

3. Results

3.1. Patient disposition and baseline demographics

A total of 139 patients were screened for the study and 114 were enrolled in the titration phase (Fig. 1). Of these 114 patients, 113 took study medication and were included in the safety population. The mean ± SE age of this group was 53.8 ± 1.1, 53.1% were male, and 68.1% were Caucasian (Table 1).

Eighty-three patients (73.5%) identified an effective and tolerable FPNS dose during the titration phase and 31 discontinued the study, including seven who withdrew for lack of efficacy; six who withdrew because of AEs, and five who withdrew consent. The remaining 13 were either lost to follow-up, did not continue to meet study requirements, violated protocol, or had another reason to discontinue.

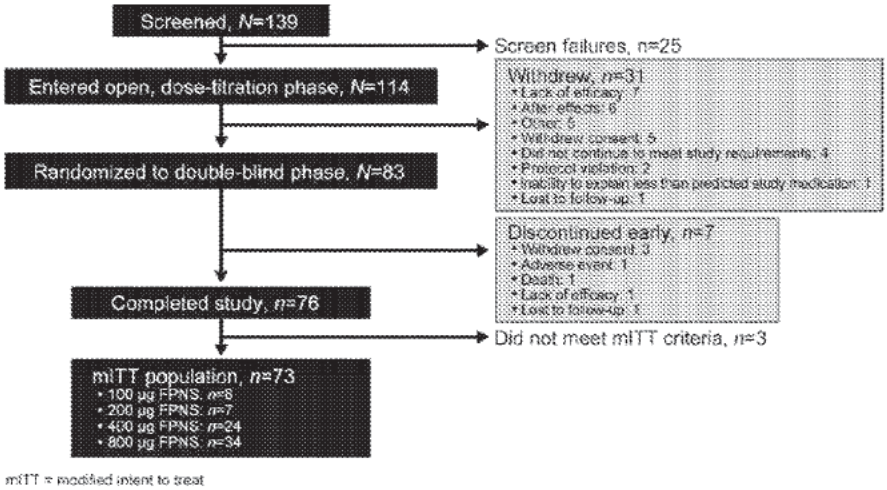

Fig. 1. Patient disposition. FPNS = Fentanyl Pectin Nasal Spray.

Table 1
Baseline demographics.

Parameter	Summary statistics ($N = 113$)
Age (years) mean ± SE (range)	53.8 ± 1.1 [21–86]
Race, *n* (%)	
Caucasian	77 (68.1)
Black	13 (11.5)
Southeast Asian	2 (1.8)
Other	21 (18.6)
% Male	53.1
Weight (kg), mean ± SE (range)	78.8 ± 1.7 [45.0–147.7]
Primary tumor type	($N = 139$)[a]
Breast	24 (17.3)
Lung	18 (12.9)
Reticuloendothelial	17 (12.2)
Bowel	16 (11.5)
Prostate	9 (6.5)
Musculoskeletal	7 (5.0)
Primary not specified/known	7 (5.0)
Upper gastrointestinal	5 (3.6)
Pancreas	4 (2.9)
Renal	4 (2.9)
Throat	4 (2.9)
CNS	4 (2.9)
Ovary	4 (2.9)
Uterus	3 (2.6)
Primary hepatic	3 (2.6)
Cervix	2 (1.4)
Testicular	2 (1.4)
Melanoma	2 (1.4)
Neuroendocrine	2 (1.4)
Bladder	2 (1.4)
Opioid use, *n* (%)[b]	
Acetaminophin-propoxyphene	1 (0.9)
Methadone/methadone hydrochloride	23 (20.4)
Hydromorphone	7 (6.2)
Morphine	45 (39.9)
Oxycodone-acetaminophen	9 (8.0)
Oxycodone	26 (23.0)
Hydrocodone bitartrate-acetaminophen	7 (6.2)
Hydrocodone	5 (4.4)
Tramadol	1 (0.9)
Fentanyl	27 (23.9)
Eastern Cooperative Oncology Group (ECOG) scores, *n* (%)	
0	10 (13.7)
1	42 (57.5)
2	21 (28.8)

[a] Data for the population screened.
[b] Some subjects used >1 opioid medication.

The most common opioids used for background pain were morphine, fentanyl, oxycodone, and methadone (Table 1). Many patients (26%) were taking multiple opioid medications. Of the 83 patients who were successfully titrated, a subset of 28 patients was taking only morphine; in this group, the mean dose was 252.9 mg (range, 60–1200 mg).

Of the 83 patients who identified an effective FPNS dose and proceeded into the double-blind phase, 76 (91.6%) completed the study (Fig. 1). Of the seven patients who discontinued during the double-blind phase, three withdrew consent and one each discontinued due to AEs, lack of efficacy, lost to follow-up and patient death, respectively.

Seventy-three of the 76 patients who completed the study met criteria for inclusion in the modified ITT population. This included 8 (11.0%) who found that the effective dose was 100 μg, 7 (9.6%) who required 200 μg, 24 (32.9%) who required 400 μg, and 34 (46.6%) who required 800 μg. The patients in the modified ITT population had a median number of BTCP episodes per day of 3 (range 1–25); all reported that the BTCP episodes were characterized by moderate or severe pain. A total of 459 BTCP episodes were treated with FPNS and 200 episodes were treated with placebo.

3.2. Efficacy

The analysis of the primary endpoint – patient-averaged SPID30 – revealed a significant difference between episodes treated with FPNS and episodes treated with placebo. The mean ± SD was 6.57 ± 4.99 for FPNS doses and 4.45 ± 5.51 for placebo (mean ± SD treatment difference 2.12 ± 3.91, $P < 0.0001$; 95% CI, 1.21–3.03). As depicted in Fig. 2, the mean SPID scores were significantly higher for FPNS than for placebo at each time point from 10 min through 60 min after the dose of study medication.

Mean baseline PI scores for patient-averaged FPNS-treated and placebo-treated episodes were comparable (6.89 versus 6.96, respectively). The mean PI score for patient-averaged FPNS-treated episodes was significantly different from that for placebo-treated episodes at the 5-min time point ($P = 0.03$), and this difference in pain was sustained over subsequent time points (Fig. 3A). The analysis of patient-averaged PID scores (Fig. 3B) showed a trend in favor of FPNS at 5 min ($P = 0.07$) and statistical significance from 10 min ($P < 0.01$) onward. Similarly, patient-averaged mean differences in PR (Supplementary Fig. 1A) and TOTPAR (Supplementary Fig. 1B) were also significant from 10 min and at all time points to 60 min.

The percentage of patients who reported a ⩾1-point reduction in PI score at each time point, comparing FPNS-treated episodes and placebo episodes, were calculated to evaluate onset of effect. At 5 min, 20.5% of patients had a ⩾1-point mean reduction in PI score following FPNS compared to 21.9% of patients following placebo ($P = 0.739$). At 10 min, 56.2% of patients following FPNS and 38.4% of patients following placebo reported this degree of relief ($P < 0.01$), and at 15 min, 72.6% of patients receiving FPNS and 52.1% of patients receiving placebo had this onset of effect ($P < 0.01$). Analysis by episodes revealed that, compared with placebo, 33% of FPNS-treated episodes showed onset of effect (⩾1-point reduction in PI) at 5 min ($P < 0.05$), 61% at 10 min, and 73% at 15 min (both $P < 0.0001$).

Evaluation of patient-level data indicated that 49% of those treated with FPNS had a clinically meaningful (⩾2-point) reduction in PI at 15 min ($P < 0.001$) and 63% had this degree of pain relief by 30 min. Evaluating these patient-level data by SPID (cumulative relief rather than relief at one point in time) demonstrated that a significantly higher percentage of patients reported a mean reduction in SPID score ⩾2 following administration of FPNS compared with administration of placebo at each time point from 10 to 60 min post dose (Supplementary Fig. 2). Evaluating this outcome at the level of each BTCP episode revealed a significant difference in favor of FPNS-treated episodes in providing a reduc-

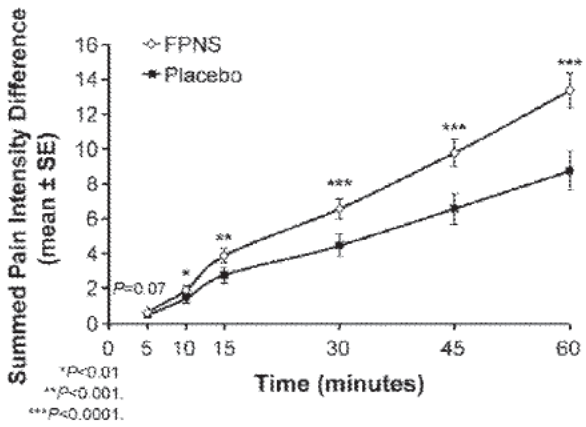

Fig. 2. SPID scores at all time points. FPNS = Fentanyl Pectin Nasal Spray.

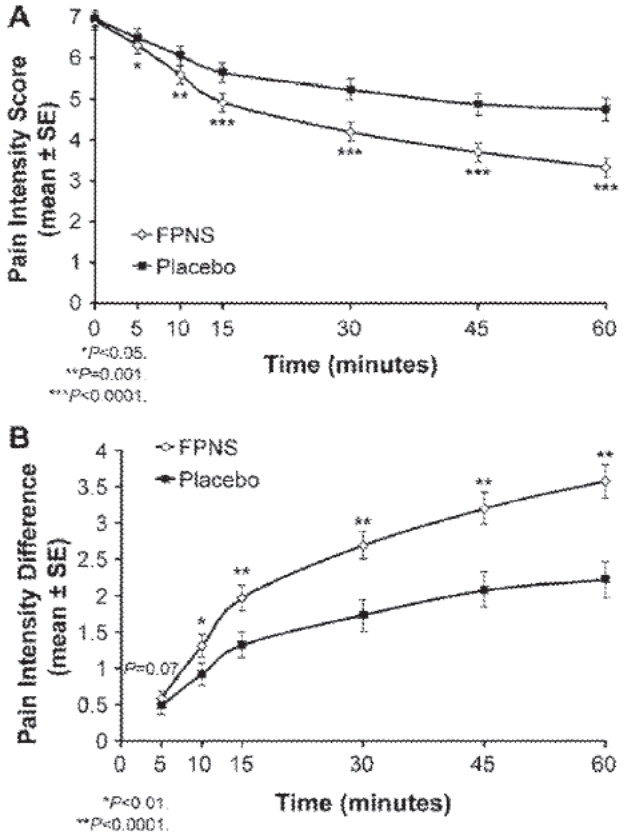

Fig. 3. Patient-averaged efficacy measures at all time points: (A) pain intensity (PI) score; (B) pain intensity difference (PID) score. FPNS = Fentanyl Pectin Nasal Spray.

tion in PI score ⩾2 at 10 min ($P = 0.01$) and at 15 min and time points thereafter ($P < 0.0001$) (Fig. 4).

3.3. Patient acceptability

Overall, 90.6% (416 of 459) of episodes treated with FPNS versus 80.0% (160 of 200) of episodes treated with placebo did not require additional rescue medication within 60 min ($P < 0.001$). No rescue medications were required following episodes with either treatment later than 60 min.

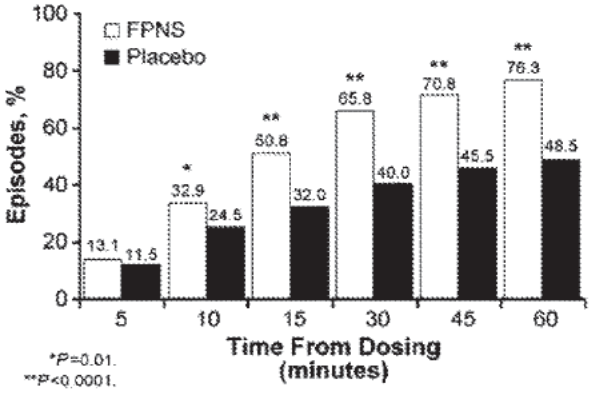

Fig. 4. Percentages of episodes with clinically meaningful pain relief (⩾2-point reduction in pain intensity). FPNS = Fentanyl Pectin Nasal Spray.

The overall mean patient-averaged acceptability assessment score was significantly greater for the active nasal spray compared with placebo at 30 min post dose (2.63 versus 2.01; $P < 0.0001$) and at 60 min post dose (2.73 versus 2.02; $P < 0.0001$). Acceptability assessments after the last treated episode demonstrated that 50 (68.5%) patients reported an overall acceptability assessment score ⩾3 (satisfied to very satisfied) for the ease of use, and 51 (69.9%) patients reported an overall acceptability assessment score ⩾3 for convenience with the nasal spray (Supplementary Fig. 3). In total, 87% of patients opted to continue FPNS into a long-term, open-label safety study.

3.4. Safety and tolerability

Treatment-related AEs were more frequent with FPNS than placebo and were mainly consistent with the pharmacologic effects of fentanyl. They were mostly mild to moderate in severity and did not increase in frequency or severity with increasing dose. Table 2 shows the most common treatment-emergent AEs in all phases. Overall, 14 serious AEs (eight following last treatment with FPNS and six following last treatment with placebo) were reported by nine patients during this study. There was no apparent relationship between FPNS dose and the serious AEs (100 μg, $n = 5$; 200 μg, $n = 1$; 400 μg, $n = 1$; 800 μg, $n = 0$). Except for the event of noncardiac chest pain, which followed last treatment with FPNS, all events were considered by the investigators working directly with the patients to be unrelated to study drug. Eight deaths occurred during the study (from screening to 1 month after completion). Four patients died during the screening period prior to taking any study drug. Of the remaining four patients, two died during the open dose-titration phase, one died during the double-blind phase and one died within a month of completing this study. None of the deaths were assessed by the investigators as related to study drug. Overall, nine patients (eight patients following last treatment with FPNS and one patient following last treatment with placebo) reported 16 treatment-emergent AEs resulting in study drug discontinuation. No patients were suspected of abuse or diversion by investigators at any of the centers involved in the trial.

There were no changes on objective clinical assessment of the nose to suggest tolerability problems with FPNS over periods of up to 4 weeks. No patient in the safety population reported any nasal problems of severe intensity either before the first use of study drug or at the final study visit. For each item, fewer than 10 patients reported nasal tolerability events of mild or moderate intensity. Mean symptom scores were extremely low (<0.2), however, and no clinically significant differences were noted between FPNS- and placebo-treated episodes.

4. Discussion

This is the first study to examine the efficacy, safety, and tolerability of FPNS in the treatment of BTCP. The study met its primary endpoint: FPNS was efficacious for pain, as indicated by a statistically significant improvement in SPID30 compared with placebo ($P < 0.0001$). Moreover, statistically significant differences in pain scores were reported with FPNS compared with placebo within 5 min of dosing, and significant improvements in pain versus placebo were maintained for 60 min after dosing.

At present, the usual approach to the treatment of BTCP involves the supplemental administration of an oral immediate-release opioid formulation, typically morphine or oxycodone. The time-action relationship of these drugs – which is characterized by an onset that may be delayed for 20 min or more, a peak that occurs at about 1 h, and a duration of effect that may extend for many hours [1,4] – may be unable to provide optimal effectiveness

Table 2
Treatment-emergent adverse events (TEAEs)[a] by type (all phases).

TEAEs, *n* (%)[a]	Fentanyl Pectin Nasal Spray Number of TEAEs[a] (%)					Placebo (*n* = 78)
	100 μg (*n* = 95)	200 μg (*n* = 82)	400 μg (*n* = 78)	800 μg (*n* = 53)	All (*n* = 113)	
Vomiting	6 (6.3)	1 (1.2)	4 (5.1)	1 (1.9)	12 (10.6)	0 (0)
Nausea	5 (5.3)	3 (3.7)	2 (2.6)	0 (0)	10 (8.8)	0 (0)
Dizziness	5 (5.3)	3 (3.7)	1 (1.3)	1 (1.9)	9 (8.0)	0 (0)
Disease progression	2 (2.1)	0 (0)	0 (0)	3 (5.7)	5 (4.4)	0 (0)
Epistaxis	1 (1.1)	2 (2.4)	2 (2.6)	2 (3.8)	5 (4.4)	0 (0)
Headache	3 (3.2)	1 (1.2)	0 (0)	0 (0)	4 (3.5)	0 (0)
Nasopharyngitis	2 (2.1)	0 (0)	0 (0)	2 (3.8)	4 (3.5)	0 (0)
Somnolence	2 (2.1)	2 (2.4)	1 (1.3)	1 (1.9)	4 (3.5)	0 (0)
Dysgeusia	2 (2.1)	0 (0)	1 (1.3)	0 (0)	3 (2.7)	0 (0)
Overall (all AEs)	31 (32.6)	11 (13.4)	16 (20.5)	16 (30.2)	58 (51.3)	4 (5.1)

[a] Treatment assignment was to the most recent active breakthrough cancer pain treatment within the previous 24 h or to placebo if no active breakthrough cancer pain treatment had been taken.

when treating a BTCP that has a more rapid onset and briefer duration. This mismatch between the pharmacodynamics of conventionally used oral rescue medications and the rapid onset and short duration of a typical BTCP episode has been the impetus for the development of new drug formulations designed to provide a more rapid onset of analgesia and duration of action that may be more consistent with the temporal profile of a typical BTCP. Most of these formulations have been based on the delivery of the lipophilic opioid fentanyl through mucous membranes. Commercially available transmucosal fentanyl formulations for BTCP deliver the opioid in the mouth, through buccal, gingival, or sublingual mucosa, and have been able to achieve onsets substantially more rapid than is possible with a standard orally administered opioid [3,14,22–24].

A goal of drug development programs for BTCP has been to achieve progressively more rapid onsets of action on the assumption that the typical BTCP episode, which usually has an onset over just a few minutes, would be optimally treated, in at least some patients, using a formulation that can produce meaningful effects in the same time frame. This is the first study of a transmucosal fentanyl formulation to observe significant relief from pain relative to placebo as early as 5 min. From the 10-min time point onward, FPNS was significantly better than placebo in several measures of PI and PR, and these differences were maintained for at least 60 min. Using a commonly accepted metric of a ⩾2-point reduction in PI as an indicator of a clinically meaningful response [9], 33% of episodes had this level of relief within 10 min of a FPNS dose and 51% experienced it by 15 min. These analyses confirm the efficacy of FPNS and provide a foundation for predicting the outcomes that are most likely to be clinically favorable, at least for patients whose episodes of BTCP are characterized by onset over a few minutes.

Overall, more treatment-emergent AEs were reported following FPNS treatment than following placebo, but no dose-dependent pattern could be identified. The most commonly reported AEs associated with FPNS were consistent with opioid treatment and were mild to moderate in severity. It is difficult to determine whether these events were caused by the treatment of BTCP or by their fixed-schedule opioid. More specifically, treatment assignment was to the most recent active BTCP treatment within the previous 24 h or to placebo if no active BTCP treatment had been taken. The four deaths recorded following receipt of study drug were classified by the investigators as associated with the progression of disease and not related to study drug.

When questioned about the acceptability of different routes of administration of analgesia for BTCP, patients in one survey indicated that they feared that the nasal route would be difficult to administer, catch in the throat, or have a bad taste, and that they were unfamiliar with the idea [28]. The results of this study refuted these concerns, demonstrating that FPNS caused no significant nasal-related symptoms, as assessed by both objective examination and subjective recording, and the majority of patients rated FPNS as easy to use and convenient. The assessment specifically included items on nasal drip and taste disturbances. The nasal route may be an alternative for patients with advanced cancer who find oral administration difficult and/or uncomfortable due to oral problems such as xerostomia, mucositis, or previous surgery [7,8,11].

The design of this study was comparable to that employed in trials to evaluate the efficacy and safety of other fentanyl formulations for BTCP. Although the use of an open-label dose-titration phase to identify a tolerable but effective dose (an enrichment approach) has been criticized [15,25], its feasibility and robustness have allowed the development of a class of rapid onset drugs for BTCP, and the enrichment itself may increase the relevance to clinical practice, during which patients' doses are titrated to yield the best outcome possible. Almost three-quarters (72.8%) of patients were able to find an effective dose during open-label titration (only 6% failed to do so because of lack of efficacy), indicating that the enrichment process did not exclude a large nonresponding group.

The study had several limitations, and the data must be interpreted appropriately. As in previous trials of BTCP [23,24], a high placebo response was noted; 80% of episodes treated with placebo did not require additional rescue medication within 60 min. Although it is possible that a significant proportion of episodes could have resolved spontaneously within only a short time, the median duration of a BTCP episode has recently been reported to be approximately 45 min [19]. It is therefore less likely that the episodes resolved within the first 5–10 min, and spontaneous resolution of the pain is less likely to have affected the early results. 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) that is subsequently maintained during placebo analgesia [18,29].

Similar to all other efficacy trials for new treatments of BTCP, this study selected patients with painful episodes likely to provide meaningful data. Patients were studied for a short period overall and the multiple-crossover design meant that there were relatively brief periods between blinded doses, which complicates efforts to identify and interpret the relationship of emergent AEs to treatment. Although the study demonstrates the efficacy and safety of FPNS within a clinical trial, the design was not intended to address the important question of clinical "effectiveness". However, effectiveness is suggested by the observation that 87% of patients opted to continue FPNS in an open-label extension phase. The extent to which this acceptability would be meaningful over time in the

larger population will require additional studies. Furthermore, the low use of additional rescue medication (9% with FPNS versus 20% with placebo) is similar or lower than other studies [13,21] and also suggests benefit from the drug. Again however, this suggestion of benefit requires confirmation in studies of comparative effectiveness.

This short-term study demonstrates that FPNS is efficacious, safe, and well tolerated for the treatment of breakthrough pain in a population of cancer patients receiving long-acting opioid treatment for chronic cancer-related pain. A rapid onset of effect was observed, with FPNS achieving statistically significant differences in PI 5 min after dosing and a ⩾2-point reduction in PI from 10 min after dosing until the end of the 60-min observation period. These findings support the use of FPNS in the treatment of BTCP.

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In the past year, R.K.P. has also served as a consultant for Ameritox, Cephalon, CNSBio, Grupo Ferrer, Nicox, Purdue Pharma, and Xenon, and his department has received research grants from Archimedes Pharmaceuticals, Baxter Healthcare Corporation, Cephalon, Forest Laboratories, Tempurpedic, and Wyeth, G.W. Pharmaceuticals, King Pharma, Pfizer Inc, Purdue, Tempur-Pedic Corporation, United BioSource Corp., and Wyeth. In the past year, A.W.B. has also received research grants from Medtronic and has served on the speakers bureau of Elan. N.G. and D.T. have no other disclosures to report for the past year.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.pain.2010.07.028.

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