Fentanyl Buccal Tablet Compared with Immediate-Release Oxycodone for the Management of Breakthrough Pain in Opioid-Tolerant Patients with Chronic Cancer and Noncancer Pain: A Randomized, Double-Blind, Crossover Study Followed by a 12-Week Open-Label Phase to Evaluate Patient Outcomes

Lynn R. Webster, MD,* Kieran A. Slevin, MD,† Arvind Narayana, MD, MBA,‡ Craig Q. Earl, PhD,§ and Ronghua Yang, PhD‡

* CRI Lifetree, Salt Lake City, Utah; † Virtua Pain and Spine Specialists, Voorhees, New Jersey (formerly of Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania); ‡ Teva Pharmaceuticals, Frazer, Pennsylvania; § Formerly of Teva Pharmaceuticals, Frazer, Pennsylvania, USA

Reprint requests to: Lynn R. Webster, MD, CRI Lifetree, 3838 South 700 East, Suite 200, Salt Lake City, UT 84106, USA. Tel: 801-261-4988; Fax: 801-261-3341; E-mail: lrwebstermd@gmail.com.

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Conflict of interest statement
L. R. Webster consults, advises, and conducts research for Teva Pharmaceuticals. K. A. Slevin has no conflicts of interest to declare. A. Narayana and R. Yang are employees of Teva Pharmaceuticals. At the time of the study, C. Q. Earl was an employee of Cephalon, Inc., now Teva Pharmaceuticals.

Abstract
Objective. Evaluate analgesic efficacy, functional benefit, and patient satisfaction with fentanyl buccal tablet vs immediate-release oxycodone for breakthrough pain (BTP).

Design. Randomized, double-blind, active-controlled crossover trial and 12-week open-label extension.

Setting. Forty-two U.S. sites.

Patients. Opioid-tolerant patients with predominantly chronic noncancer pain experiencing BTP.

Intervention. Patients were randomized to open-label titration periods with fentanyl buccal tablet followed by oxycodone or vice versa for BTP management. After titrating to a successful dose of both medications (single dose providing adequate analgesia without unacceptable adverse events), patients were re-randomized to treat 10 BTP episodes with one medication and 10 with the other.

Outcome Measures. The primary efficacy measure was pain intensity (PI) difference 15 minutes postdose. Secondary measures included PI difference 5, 10, 30, 45, and 60 minutes postdose; sum of PI differences 30 and 60 minutes postdose; ≥33% and ≥50% reduction in PI; and pain relief. Questionnaires assessed functional status/satisfaction.

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Results. Of 213 patients enrolled, 149 achieved a successful dose of both medications; 131 completed the double-blind phase and 112 the open-label phase. PI difference at 15 minutes (mean [standard deviation]) was greater with fentanyl buccal tablet (0.88 [1.20]) vs oxycodone (0.76 [1.13]; \( P < 0.001 \)). Patients preferred fentanyl buccal tablet (47%) over oxycodone (35%); 18% had no preference. Patients and clinicians reported consistently better functional improvement and satisfaction with fentanyl buccal tablet vs short-acting opioids (\( P < 0.05 \)).

Conclusions. Fentanyl buccal tablet was associated with rapid onset of analgesia and improvements in functional status and patient satisfaction compared with immediate-release oxycodone.

Key Words. Breakthrough Pain; Fentanyl Buccal Tablet; Opioid Tolerant; Oxycodone

Introduction

Breakthrough pain (BTP), a transitory exacerbation of pain that occurs on a background of otherwise controlled, persistent pain [1], is highly prevalent among patients with chronic pain. In studies of patients with chronic cancer pain, 33–89% of patients with controlled, persistent pain reported experiencing BTP [1–4]. Similarly, in surveys of patients with chronic noncancer pain, BTP was reported in 48–74% of patients and had characteristics comparable with those reported in the cancer population [4–6]. BTP episodes often reach peak intensity within 10 minutes [1,2,4,5,7], indicating the need for effective analgesic agents with fast onset of action. Although orally administered short-acting opioids (SAOs [e.g., oxycodone and hydrocodone]) are often prescribed for the management of BTP [1,8,9], the time course for clinically relevant analgesia with these agents (~30–60 minutes) may occur after the time of peak intensity for many BTP episodes [2,7,9].

Fentanyl buccal tablet is a rapid-onset opioid indicated for the management of BTP in adults with cancer who are opioid tolerant [10]. Transmucosal delivery of fentanyl allows for rapid fentanyl absorption across the buccal mucosa [11]. Studies have shown that fentanyl buccal tablet is effective for the management of BTP and is generally well tolerated [12–19].

Data are limited regarding the comparative effectiveness of rapid-onset opioids, such as fentanyl buccal tablet, vs SAOs. Clinical guidelines have recently identified the need for head-to-head studies investigating the analgesic efficacy and functional improvements associated with different treatments for BTP to guide evidence-based treatment decisions [8,20]. Currently, no validated tool for the assessment of functioning in patients with BTP exists. In a previous study assessing the efficacy and safety of fentanyl buccal tablet vs immediate-release oxycodone for the management of BTP in opioid-tolerant patients with chronic pain, fentanyl buccal tablet was associated with a more rapid onset of analgesia than immediate-release oxycodone; however, functional improvement was not assessed [17]. This is the second study designed to compare the efficacy and safety of a rapid-onset opioid (fentanyl buccal tablet) with a traditional SAO (immediate-release oxycodone), both titrated to a successful dose, for the treatment of BTP in opioid-tolerant patients with chronic pain. This study included a 12-week open-label extension, during which functional improvement and patient satisfaction were assessed.

Methods

This randomized, double-blind, active-controlled crossover study, followed by a 12-week open-label extension, evaluated the efficacy and safety of fentanyl buccal tablet compared with immediate-release oxycodone for the management of BTP in opioid-tolerant patients with chronic pain of cancer or noncancer origin. The study was conducted at 42 sites in the United States from December 2008 to November 2009 (U.S. National Institutes of Health Identifier, NCT00813488). The protocol was approved by an institutional review board or independent ethics committee at each study site, and all study procedures were conducted in accordance with good clinical practice [21]. Written informed consent was obtained from all patients before study enrollment.

Patients

Men and women between 18 and 80 years of age were eligible for inclusion in the study if they: 1) had a ≥3-month history of chronic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, traumatic injury, complex regional pain syndrome, back pain, neck pain, fibromyalgia, chronic pancreatitis, osteoarthritis, rheumatoid arthritis, or cancer; 2) were opioid tolerant (i.e., were taking at least 60 mg/day of oral morphine or the equivalent of another opioid as an around-the-clock [ATC] opioid for ≥1 week before study entry); 3) had an average pain intensity (PI) score of ≤6 on an 11-point numeric rating scale (0 = no pain, 10 = worse pain imaginable); and 4) were experiencing one to four episodes of BTP per day (lasting <4 hours on average) and were achieving at least partial relief with opioids for their BTP.

Exclusion criteria were uncontrolled or rapidly escalating pain that was not BTP, known allergy or contraindication to any ingredient in the study medication, recent history (within the past 5 years) of alcohol or substance abuse, a positive urine drug screening test for an illicit drug or medication, diagnosis of chronic headache or migraine as the primary painful condition, presence of cardiopulmonary disease or other medical/psychiatric disorder that could significantly increase the risks associated with opioid treatment or compromise study data, history of...
suicide attempt or suicidal ideation, pregnancy or lactation, participation in a previous fentanyl buccal tablet study, or participation in a study involving an investigational drug in the previous 30 days.

Study Design

This crossover study included a screening period, two open-label titration periods (up to 17 days), and two double-blind treatment periods (up to 21 days), followed by a 12-week open-label extension (Figure 1). Detailed methodology for the screening period, open-label titration periods, and double-blind treatment periods have been previously reported by Ashburn et al. in a separate study with an identical study design [17], except for the additional open-label extension phase in the current study. In brief, patients were assessed for participation and baseline data were collected during the screening period. During the open-label titration periods, each patient identified a successful dose of fentanyl buccal tablet (200, 400, 600, or 800 mg) and immediate-release oxycodone (15, 30, 45, or 60 mg) in a randomized order. A successful dose was defined as the single dose strength at which the patient reported adequate pain relief (PR) for at least two of three BTP episodes without requiring supplemental medication and without experiencing unacceptable adverse events (AEs). Patients were then randomized to treat 10 BTP episodes with one of the two blinded study medications at the identified successful dose during the first double-blind treatment period and then to manage a subsequent 10 episodes of BTP with the other blinded study medication during the second double-blind treatment period. Patients served as their own controls; treatment comparisons were made within patients. A double-dummy treatment technique was used to maintain blinding; patients took an oral capsule first and then a buccal tablet for each BTP episode (i.e., one active treatment and one matching placebo for the other study medication). Once patients administered the study medication, they were not permitted to administer any other study medications for at least 4 hours and could not take pre-study supplemental medication for at least 60 minutes.

Patients successfully completing the double-blind phase of the study were eligible to enroll in the 12-week open-label extension and were randomized to continue fentanyl buccal tablet treatment or to begin treatment with any traditional SAO deemed appropriate by their treating physician. Patients randomized to fentanyl buccal tablet were not permitted to take any other supplemental medication for their BTP, but were allowed to take a second dose of fentanyl buccal tablet if there was insufficient relief of the BTP episode after 30 minutes. They were instructed to treat no more than six BTP episodes per day with no more than eight doses of fentanyl buccal tablet per day. Patients randomized to a traditional SAO were permitted to take any supplemental medication prescribed by their physician (with the exception of oral transmucosal fentanyl citrate and fentanyl buccal tablet).

Assessments

The primary efficacy measure was the difference in PI (rated on an 11-point numeric scale: 0 = no pain, 10 = worst pain imaginable) before and 15 minutes after (PID15) administration of study medication. Other efficacy measures included PID at 5, 10, 30, 45, and 60 minutes after administration of study medication; summed PID from 5 through 30 minutes (SPID30) and from 5 through 60 minutes (SPID60) after administration of study medication; PR measured on a five-point numeric scale (0 = none, 4 = complete PR) at 5, 10, 15, 30, 45, and 60 minutes.

Figure 1  Study design. This crossover study included a screening period, two open-label titration periods, and two double-blind treatment periods, followed by a 12-week open-label extension. OxyIR = immediate-release oxycodone; SAO = short-acting opioid.
after administration of study medication; time from admin- 
istration of study medication to meaningful PR; total PR at 60 minutes (TOTPAR60); and the proportion of BTP episodes with an improvement in PI of ≥33% (i.e., moderate improvement) and ≥50% (i.e., substantial improvement) at 5, 10, 15, 30, 45, and 60 minutes after study medication [22,23]. A medication performance assessment was completed at 30 and 60 minutes after administration of each study medication. The patient was asked “How well did your study medication perform in controlling this BTP episode?” and the answers were summarized on a five-point numeric scale (0 = poor, 4 = excellent). After the second double-blind treatment period, patients completed a medication preference questionnaire that asked them which medications they preferred to treat their pain flares: the study medication administered in the first double-blind treatment period, the study medication administered in the second double-blind treatment period, or no preference. Patients completed electronic diaries for efficacy measures assessed during the open-label titration and double-blind treatment periods. During the 12-week extension, paper diaries were used to record the number of BTP episodes experienced, the number of BTP episodes requiring treatment with study medication, and the number of tablets taken. For the first five BTP episodes after each visit, patients also recorded PI before study medication administration and a medication performance assessment 30 and 60 minutes after study medication administration.

Functional improvement and change in overall patient status were evaluated during and/or after the open-label extension through the use of the Patient Assessment of Function (PAF), Clinician Assessment of Patient Function (CAPF), Patient Global Impression of Change (PGIC), and Clinical Global Impression of Change (CGIC) questionnaires. The PAF and CAPF questionnaires were completed at weeks 4, 8, and 12 of the open-label extension and were used to measure a patient’s ability to function in the course of normal activities. Answers on the PAF and CAPF were rated on a seven-point numeric scale (1 = very much worsened, 7 = very much improved). The PGIC and the CGIC questionnaires were completed at weeks 4, 8, and 12 of the open-label extension. The PGIC was used to measure the patient’s global impression of improvement in pain, and the CGIC was used to measure the clinician’s global impression of improvement in patients’ pain beginning from the start of the open-label extension. Answers to the PGIC and CGIC were based on a seven-point numeric scale (−3 = very much worse to +3 = very much improved).

Safety and tolerability were monitored throughout the study by assessing reports of any AEs, including serious AEs and discontinuations due to AEs, physical examinations, including changes in the oral mucosa and vital sign measurements, as well as clinical laboratory tests.

Statistical Analysis

A detailed description of the data analyses for the efficacy measures during the double-blind treatment period have been previously reported [17]. The planned number of patients for enrollment in this study was originally 383 patients in order to have 230 evaluable patients. However, the planned sample size estimate for this study was decreased to 175 patients based on data from the previous study [17]. An estimated 105 evaluable patients were needed to achieve a 90% power for the primary efficacy analysis (paired t-test, two sided, alpha = 0.05). For the primary efficacy measure and secondary assessments of PID, data for fentanyl buccal tablet and immediate-release oxycodone were compared using an analysis of variance model, with treatment, period, and treatment sequence as fixed effects and patient as a random effect. PR was assessed using the Wilcoxon’s signed rank test.

Patients were randomized to one of the two treatment sequences through an interactive voice response system. Randomization was stratified by the primary chronic pain diagnosis of either low back pain or all other pain to ensure balance among the different sequences.

The double-blind efficacy analysis set, which included all patients who had at least one evaluable episode of BTP treated with fentanyl buccal tablet and at least one evaluable episode of BTP treated with immediate-release oxycodone, was used for analyses of the primary and secondary pain assessments. The open-label efficacy assessment set, which included all patients in the open-label safety analysis set who were randomly assigned to open-label treatments, took at least one dose of the study medication, and had at least one assessment for at least one of the questionnaires, was used to summarize outcomes on the PAF, CAPF, PGIC, and CGIC questionnaires. Functional assessment data were summarized using descriptive statistics, and Pearson’s correlation tests were performed to assess any associations between PAF and CAPF, and between PGIC and CGIC by treatment for each visit.

All patients who took at least one dose of study medication were included in the open-label titration, double-blind, and open-label treatment safety analyses. AEs were summarized by treatment. Safety comparisons were descriptive, and no formal statistical testing was performed.

Results

Patients

In total, 307 patients were screened, and 213 were enrolled in the study. Of these, 211 entered the titration phase, received at least one dose of fentanyl buccal tablet or immediate-release oxycodone, and were evaluable for safety. A total of 149 (71%) patients found a successful dose for both drugs; 143 (68%) patients completed both open-label titration periods and entered the double-blind treatment periods, and 137 patients were evaluable for
efficacy. Of the 131 patients who completed both double-blind treatment periods and entered the open-label extension, 112 (85%) completed the open-label extension (Figure 2).

Patient demographics and other baseline characteristics of the enrolled, the double-blind efficacy, and the open-label extension populations were similar (Table 1). The mean age of enrolled patients was 51 years; 68% entered the study with back pain as their primary diagnosis of chronic pain. The dose and type of ATC opioid and supplemental opioid medications at baseline for treated patients are presented in Table 2. In addition to analgesics, the concomitant medications most frequently taken by patients in the safety analysis set included psychoanalytics such as psychostimulants and antidepressants (65%), psycholeptics such as benzodiazepines and antipsychotic medications (60%), and muscle relaxants (39%).

Overall, 166 (79%) of 211 patients who entered the dose titration phase found a successful dose of fentanyl buccal tablet (16% identified 200 μg, 18% identified 400 μg, 20% identified 600 μg, 25% identified 800 μg, and 21% did not find or document a successful dose), and 156 (74%) of 211 patients found a successful dose of immediate-release oxycodone (17% identified 15 mg, 19% identified 30 mg, 21% identified 45 mg, 17% identified 60 mg, and 27% did not find or document a successful dose). Based on the distribution of successful doses, there was a clear relationship between the successful dose of fentanyl buccal tablet and the successful dose of immediate-release oxycodone; patients who required the higher doses of fentanyl buccal tablet (i.e., 600 or 800 μg) generally tended to need the higher doses of immediate-release oxycodone (i.e., 45 or 60 mg) as their successful dose.

Figure 2 Patient disposition. The safety analysis set for the open-label titration periods, double-blind treatment periods, and the open-label extension period included all patients treated with at least one dose of study medication.
No linear relationship was observed with regard to the successful doses of fentanyl buccal tablet or immediate-release oxycodone achieved during the titration phase and the ATC or supplemental opioid medication dose at baseline. Of the 26 patients who found a successful dose and were taking pure oxycodone (i.e., not a combination product) as their supplemental opioid at baseline, 22 (85%) were taking daily doses of $15 \text{ mg per episode}$ at baseline. After titration, 68% of these patients found a successful immediate-release oxycodone dose of $30 \text{ mg}$.

### Efficacy

During the double-blind treatment periods, the primary efficacy measure, mean (standard deviation) PID$_{15}$ score was significantly greater after fentanyl buccal tablet administration ($0.88 \pm 1.20$) than after immediate-release oxycodone ($0.76 \pm 1.13$; $P < 0.001$). The mean PID also was significantly greater after fentanyl buccal tablet administration compared with immediate-release oxycodone beginning as early as 10 minutes postdose ($P = 0.01$), and a significant difference was maintained through 60 minutes ($P < 0.001$; Figure 3).

Mean values of patient assessments of PR were significantly greater after fentanyl buccal tablet administration than after immediate-release oxycodone administration beginning at 15 minutes ($P = 0.04$) and at all subsequent time points ($P < 0.01$; Figure 4). Fentanyl buccal tablet was shown to be more effective than immediate-release oxycodone, as reflected in several of the secondary efficacy measures (Table 3). Any PR was achieved in a significantly higher percentage of BTP episodes treated with fentanyl buccal tablet compared with immediate-release oxycodone beginning at $15 \text{ minutes}$ through $45 \text{ minutes}$ postdose. Mean TOTPAR$_{60}$ was significantly greater after fentanyl buccal tablet administration than with immediate-release oxycodone.

The percentage of BTP episodes for which patients reported an improvement in PI of $33\%$ was greater with fentanyl buccal tablet compared with...
## Table 2  Around-the-clock* and rescue opioid regimens at baseline

| Variable | 
|-------------------------|-------------------------|
| **Around-the-clock opioids** | 
| Patients taking oral opioids at baseline (N = 162), mg/day | Mean (SD) 193.8 (163.3) |
| | Median (range) 120.0 (30.0–960.0) |
| Patients taking transdermal fentanyl (N = 44), μg/hour | Mean (SD) 76.1 (31.9) |
| | Median (range) 75.0 (25.0–150.0) |
| Patients taking intrathecal medications (N = 6)§ | 
| Type of around-the-clock opioid at baseline, N (%) | 
| Oxycodone | 64 (30) |
| Morphine | 60 (28) |
| Fentanyl | 44 (21) |
| Hydrocodone | 25 (12) |
| Methadone | 14 (7) |
| Oxymorphone | 10 (5) |
| Hydromorphone | 2 (<1) |
| Tramadol | 1 (<1) |
| **Rescue opioids** | 
| Patients taking oral opioids (N = 162), mg/episode of BTP† | Mean (SD) 20.5 (19.2) |
| | Median (range) 15.0 (3.8–160.0) |
| Patients taking transdermal fentanyl (N = 44) | Mean (SD) 22.7 (20.1) |
| | Median (range) 15.0 (3.8–120.0) |
| Patients taking intrathecal medications (N = 6)§ | 
| Type of supplemental opioid at baseline, N (%) | 
| Oxycodone | 93 (44) |
| Hydrocodone | 69 (32) |
| Morphine | 21 (10) |
| Hydromorphone | 16 (8) |
| Tramadol | 8 (4) |
| Propoxyphene | 7 (3) |
| Oxymorphone | 6 (3) |
| Fentanyl | 1 (<1) |

* One patient was not taking an around-the-clock medication at baseline, in violation of the study protocol.
† All milligrams were measured in oral morphine equivalents.
‡ Oral around-the-clock medications taken in addition to transdermal fentanyl were excluded.
§ Intrathecal around-the-clock medications were not converted to oral morphine equivalents.
BTP = breakthrough pain; SD = standard deviation.

The distribution of responses on the patients’ assessment of medication performance significantly favored fentanyl buccal tablet (\(P < 0.001\)). At 30 minutes postdose, patients rated medication performance as “good” to “excellent” for 41% of BTP episodes treated with fentanyl buccal tablet compared with 32% of episodes treated with immediate-release oxycodone. “Good” to “excellent” ratings were recorded at 60 minutes postdose for 78% of the episodes treated with fentanyl buccal tablet vs 74% of episodes treated with immediate-release oxycodone. On the medication preference questionnaire, 62 (47%) of 131 patients who completed both double-blind treatment periods and this questionnaire preferred fentanyl buccal tablet, and 46 (35%) preferred immediate-release oxycodone for management of their BTP: 23 patients (18%) had no preference and 12 (9%) did not complete the questionnaire.

Functioning reported by patients and by clinicians was consistently better in patients receiving fentanyl buccal tablet than in patients receiving traditional SAOs (Figures 5 and 6). More than 40% of patients reported some improvement in 10 of the 12 areas of functioning assessed by the PAF and CAPF at the final visit. At the final visit, several differences on the PAF and CAPF questionnaires were statistically significant between study groups, notably the need to change positions to relieve BTP (\(P < 0.01\)), performing usual activities at home (\(P < 0.01\)), and enjoying life (\(P < 0.001\)). In addition, a higher correlation was noted between the PAF and CAPF results in all 12 areas of functioning for patients receiving fentanyl buccal tablet (Pearson’s correlation coefficient \(r = 0.69–0.95\)) compared with those receiving traditional SAOs (\(r = 0.73–0.85\)). Responses on the PGIC and CGIC favored fentanyl buccal tablet over traditional SAOs and were statistically significant at the final visit (\(P < 0.001\); Figure 7). The correlation between the PGIC and CGIC scores for patients receiving fentanyl buccal tablet (\(r = 0.87\)) was slightly higher compared with patients receiving traditional SAOs (\(r = 0.84\)).

### Safety and Tolerability

Overall, 130 (62%) of the 211 patients who received at least one dose of study medication reported at least one AE during the study, 93 (48%) after receiving fentanyl immediate-release oxycodone at 30 and at 45 minutes (\(P < 0.05\)). The percentage of episodes reported to improve by \(\geq50\%\) was significantly greater with fentanyl buccal tablet than with immediate-release oxycodone only at 10 minutes posttreatment (\(P < 0.05\)). After administration of study medication, mean SPID\(_{60}\) and SPID\(_{90}\) were significantly greater for fentanyl buccal tablet than for immediate-release oxycodone.
buccal tablet, 75 (41%) after receiving immediate-release oxycodone, and 11 (52%) after receiving another SAO. The incidence of AEs was 42% (89/211) during the titration periods, 29% (41/143) during the double-blind treatment periods, and 52% (68/130) during the open-label extension. The most frequently reported AEs were somnolence (fentanyl buccal tablet, 4%; immediate-release oxycodone, 5%) and dizziness (fentanyl buccal tablet, 3%; immediate-release oxycodone, 3%) during the open-label titration periods; headache (fentanyl buccal tablet, 2%; immediate-release oxycodone, 1%) and back pain (fentanyl buccal tablet, 1%, immediate-release oxycodone, 2%) during the double-blind treatment periods; and back pain (fentanyl buccal tablet, 5%; traditional SAO, 8%) and vomiting (fentanyl buccal tablet, 5%; traditional SAO, 8%) during the open-label extension (Table 4). AEs involving the application site of fentanyl buccal tablet (erythema, irritation, pain, swelling, or ulcer) occurred in 18 patients throughout the study (14 events during the titration period, four during the double-blind treatment period, and two during the open-label extension); the majority (96%) of the events resolved with no residual effect.

In total, 18 (9%) patients discontinued from the study because of AEs; 13 (6%) patients in the open-label titration periods (fentanyl buccal tablet, N = 10; immediate-release oxycodone, N = 3), two (1%) patients in the double-blind treatment periods (fentanyl buccal tablet, N = 1; immediate-release oxycodone, N = 1), and three (2%) patients in the open-label extension (fentanyl buccal tablet, N = 1; traditional SAO, N = 2). The most frequent AEs leading to discontinuation were nausea, dizziness, somnolence, euphoric mood, and pruritus (N = 2 for each; all after fentanyl buccal tablet treatment), and generalized pruritus and back pain (N = 2 for each; one after fentanyl buccal tablet treatment and one after immediate-release oxycodone).

Figure 3 Pain intensity difference at each time point by treatment. *P = 0.01; †P < 0.001. OxyIR = immediate-release oxycodone; SE = standard error.

Figure 4 Pain relief at each time point by treatment. *P = 0.04; †P < 0.01. OxyIR = immediate-release oxycodone; SE = standard error.
Table 3  Summary of additional secondary efficacy outcome measures at 5 through 60 minutes after study medication administration

<table>
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<tr>
<th></th>
<th>Any PR, Episodes (%)</th>
<th>Meaningful PR, episodes (%)</th>
<th>TOTPAR, Mean (SD)</th>
<th>≥33% Improvement in PI, episodes (%)</th>
<th>≥50% Improvement in PI, episodes (%)</th>
<th>SPID, Mean (SD)</th>
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<tr>
<td></td>
<td>Fentanyl Buccal Tablet (N = 1,342)</td>
<td>OxyIR (N = 1,334)</td>
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<td>5 minutes</td>
<td>55 (4)</td>
<td>21 (2)</td>
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<td>10 minutes</td>
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<td>155 (15)</td>
<td>230 (17)</td>
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<td>30 minutes</td>
<td>1,004 (75)**</td>
<td>677 (66)</td>
<td>613 (46)**</td>
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<td>2,52 (2.13)**</td>
<td>2,16 (2.08)</td>
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<td>45 minutes</td>
<td>1,217 (91)*</td>
<td>983 (73)**</td>
<td>864 (65)</td>
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<td>60 minutes</td>
<td>[515]</td>
<td>[1,271]</td>
<td>[1,239]</td>
<td>[1,139]**</td>
<td>[1,047]</td>
<td>[6.42 (2.61)**</td>
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* P < 0.05; ** P < 0.01; *** P < 0.0001.

--- not assessed; OxyIR = immediate-release oxycodone; PI = pain intensity; PR = pain relief; SD = standard deviation; SPID = sum of pain intensity differences; TOTPAR = total pain relief.
Figure 5 Patient Assessment of Function at final visit. Fentanyl buccal tablet (FBT) (N = 65); short-acting opioid (SAO) (N = 65). *P < 0.05 for FBT vs SAO treatment comparison; †P < 0.01 for FBT vs SAO treatment comparison; ‡P = 0.001 for FBT vs SAO treatment comparison. BTP = breakthrough pain.

Figure 6 Clinician Assessment of Patient Function at final visit. Fentanyl buccal tablet (FBT) (N = 65); short-acting opioid (SAO) (N = 65). *P < 0.05 for FBT vs SAO treatment comparison; †P < 0.01 for FBT vs SAO treatment comparison; ‡P = 0.001 for FBT vs SAO treatment comparison. BTP = breakthrough pain.
Serious AEs were reported in eight patients: two during the open-label titration periods (fentanyl buccal tablet, N = 1; immediate-release oxycodone, N = 1) and six during the open-label extension (fentanyl buccal tablet, N = 3; traditional SAO, N = 3). No serious AEs occurred during the double-blind treatment periods. Two patients had serious AEs while being treated with fentanyl buccal tablet that were considered by the investigator to be possibly related or related to study medication. During the open-label titration periods, one patient had a serious AE of unresponsiveness after the consumption of two doses of fentanyl buccal tablet 800 mg and alcohol. The event was considered possibly related to study medication and resolved without sequelae; the patient discontinued participation in the study. As noted earlier, patients were excluded from the study if they had a history of current or recent abuse of alcohol but were not specifically prohibited by the protocol from drinking alcohol during this study. In addition, a serious AE of drug withdrawal syndrome was reported during the open-label extension when a patient stopped taking fentanyl buccal tablet and his ATC opioid. This event was considered related to study medication and resolved without residual effect. The patient recovered and was discontinued from the study due to noncompliance. The serious AEs reported in the other six patients were all considered by the investigator to be not related to study medication.

Discussion
The results from this randomized, double-blind, active-controlled crossover study of opioid-tolerant patients with chronic pain are consistent with results from a previous, similarly designed, head-to-head study [17]. In the treatment of BTP, onset of analgesia was more rapid after administration of fentanyl buccal tablet than after administration of immediate-release oxycodone. Statistically
significant differences between fentanyl buccal tablet and immediate-release oxycodone were observed in PID as early as 10 minutes after administration of study medication and in PR as early as 15 minutes postdose. Significant differences favoring fentanyl buccal tablet were also observed in the additional secondary efficacy measures of SPIED, the proportion of episodes with ≥33% and ≥50% reduction in PI, time to achievement of any PR or meaningful PR, TOTPAR, and the medication performance questionnaire. The results of the efficacy assessments are corroborated by findings from the BTP preference questionnaire, in which 47% of patients preferred fentanyl buccal tablet vs 35% of patients who preferred immediate-release oxycodone.

After 12 weeks of open-label treatment, patients and clinicians reported consistently better functional improvement and satisfaction with fentanyl buccal tablet compared with traditional SAOs. These findings are of particular interest given that the assessment of function in clinical studies of BTP is difficult because tools validated in chronic, persistent pain (e.g., Brief Pain Inventory-Short Form, modified Oswestry Disability Index, 36-item Short-Form Health Survey, and Profile of Mood States) have not shown substantial sensitivity in BTP [18,19]. However, BTP-specific assessments such as the PAF and CAPF questionnaires have been developed and utilized in fentanyl buccal tablet studies [19,24] and appear valid [25]. The findings in the current study for the newly developed PAF and CAPF scales are consistent at a population level with the results of the standardized PGIC and CGIC scales. In our study, PAF and CAPF correlation coefficients for assessment responses ranged between 0.69 and 0.95 for patients who received fentanyl buccal tablet and between 0.73 and 0.85 for patients who received traditional SAOs during the open-label extension. The PGIC/CIGC correlation coefficients were 0.87 for those receiving fentanyl buccal tablet and 0.84 for those receiving traditional SAOs.

Fentanyl buccal tablet and immediate-release oxycodone were generally well tolerated, and the tolerability profiles for the study medications were similar during each treatment period. The safety profile of fentanyl buccal tablet in this study was consistent with the profile observed in the study conducted by Ashburn et al. and other previous studies of fentanyl buccal tablet [12–18]. Throughout the entire study, the occurrence of nausea and dizziness was similar after fentanyl buccal tablet treatment (5% and 4%, respectively) and treatment with immediate-release oxycodone (4% each). Eighteen (9%) patients reported AEs associated with the fentanyl buccal tablet application site, but these AEs did not lead to discontinuation from the study.

Data from clinical studies assessing the comparative safety and efficacy of rapid-onset and traditional SAOs for the management of BTP are limited. Coluzzi et al. conducted a randomized, double-blind, crossover study of oral transmucosal fentanyl citrate vs immediate-release oral morphine sulfate for the treatment of BTP [26]. A limitation of the study was that immediate-release oral morphine sulfate was not titrated to a successful dose before initiation of the double-blind treatment period, thereby limiting the comparative utility of the data. Similar to the study conducted by Ashburn et al. [17], the design of the current study allowed for titration of active treatments to a successful dose before patients began double-blind treatment and selected only those patients who found a successful dose of both drugs. The percentage of patients who found a successful dose (70%) of both fentanyl buccal tablet and immediate-release oxycodone in this study was near the low end of the range observed in previous studies comparing fentanyl buccal tablet and placebo (65–81%) [12–16,18]. This was to be expected, as our study required titration of two study medications instead of one. The proportion of patients who found a successful dose of fentanyl buccal tablet during the first titration period (79%) was similar to that seen in previous studies. Lastly, differences in PID reached significance at 10 minutes in our study while in the study conducted by Ashburn et al. that had an identical study design (except for the additional open-label extension phase in the current study) and inclusion/exclusion criteria, significant differences were reached at 5 minutes [17]. This difference may be attributed to variability in patient characteristics between the two studies. Another important reason for the later statistical significance in our study may be due to the lower numbers of patients and BTP episodes. There were 137 patients with approximately 1,350 episodes in our study while the study conducted by Ashburn et al. had 183 patients with approximately 1,750 episodes [17].

These study results lead to several interesting observations regarding analgesic dosing. First, there appeared to be a clear correlation between the successful dose of fentanyl buccal tablet and the successful dose of immediate-release oxycodone for BTP, with successful doses of fentanyl buccal tablet 200, 400, 600, and 800 μg correlating with successful doses of immediate-release oxycodone 15, 30, 45, and 60 mg, respectively. There was no simple linear relationship between successful doses of fentanyl buccal tablet or immediate-release oxycodone and ATC analgesic doses, supporting the concept that BTP should be assessed and treated independently of persistent pain and the dose of ATC medication. Second, the high number of patients receiving oxycodone for BTP before the study who titrated to a higher oxycodone dose during the study suggests that BTP may be currently undermanaged. The dose of immediate-release oxycodone was lowered by investigators during the open-label extension, suggesting that the doses of oxycodone administered during the double-blind phase were higher than what is generally acceptable in clinical practice. As the study was designed to make a fair pharmacologic comparison between fentanyl buccal tablet and oxycodone, we recognize that the study titration procedures for oxycodone did not necessarily mimic typical clinical practice. As such, it would be difficult to determine whether similar results would be observed outside of a controlled study setting.
Webster et al.

Significant concern has been raised regarding the risk of abuse and diversion of opioids when used to treat chronic noncancer pain [27]. The role of rapid-onset opioids or traditional SAOs in contributing to this risk is not clear. Data regarding the occurrences of aberrant drug-related behavior in patients from the current study administering fentanyl buccal tablet or a traditional oral SAO for BTP over 12 weeks of open-label treatment have been presented elsewhere [28].

Finally, further research could be conducted to better understand subgroups of patients who would benefit the most from a rapid-onset opioid such as fentanyl buccal tablet. For instance, patients with unpredictable and/or rapid-onset BTP may have a greater benefit than those patients who do not have these particular characteristics [29]. This study, as well as a previous, similarly designed, head-to-head study [17], is the first to evaluate an important hypothesis that analgesics with greater early systemic exposure may be more suitable for patients with BTP who often have a rapid onset of their pain.

In conclusion, fentanyl buccal tablet was associated with greater PR, including a more rapid onset of analgesia, as well as better functional improvement and patient satisfaction than oxycodone for the treatment of BTP in opioid-tolerant patients with chronic pain. Safety and tolerability profiles were comparable.

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