A Randomized, Placebo-Controlled Study of a New Sublingual Formulation of Fentanyl Citrate (Fentanyl Ethypharm) for Breakthrough Pain in Opioid-Treated Patients With Cancer

Stanislava Novotna, MD¹; Klara Valentova, MD²; Jitka Fricova, MD³; Eva Richterova, MD⁴; Sarka Harabisova, MD⁵; Françoise Bullier, PharmD⁶; Françoise Trinquet, MD⁷; and on Behalf of the ETHYFYL Study Group

¹Vysokomytska nemocnice, Vysoke Myto; ²Nemocnice s poliklinikou v Semilech, Semily; ³Vseobecna fakultni nemocnice, Prague; ⁴Ambulance lecby chronice bolesti a paliativni mediciny, Hradec Kralove; ⁵Metstska nemocnice Ostrava, Ostrava, Czech Republic; ⁶ICTA PM, Fontaine les Dijon, France; ⁷Ethypharm, Saint Cloud, France

ABSTRACT

Background: Oromucosal fentanyl is currently used for the treatment of breakthrough pain (BTP) in opioid-treated cancer patients. Ethypharm developed a sublingual formulation of fentanyl suprabioavailable to oral transmucosal fentanyl citrate with a higher early systemic exposure and a shorter T_max.

Objectives: This study evaluated the efficacy and safety profile of fentanyl Ethypharm (FE) in relieving BTP in opioid-treated cancer patients.

Methods: Opioid-treated adult cancer patients, experiencing 1 to 4 episodes of BTP per day, were included in the study. After an open-label titration period to identify an optimal dose that would provide adequate pain relief for 2 consecutive episodes of BTP with an acceptable level of adverse events, patients were randomly assigned to a double-blind, placebo-controlled, crossover period with 1 of 13 prespecified sequences of 9 tablets (6 tablets of FE of the dose identified during the open-label titration and 3 placebo). Pain intensity and pain relief were recorded at 3, 6, 10, 15, 30, and 60 minutes after study drug administration. Adverse events were recorded. The primary end point was the sum of pain intensity differences (SPID) at 30 minutes.

Results: The distribution of optimal dosages of FE was as follows: 133 μg, 35.9%; 267 μg, 30.8%; 400 μg, 14.1%; 533 μg, 12.8%; and 800 μg, 6.4%. In the modified intention-to-treat population (n = 73), FE significantly improved mean (SE) SPID compared with placebo at 30 minutes (75.0 [49.8] vs 52.5 [52.8]; P < 0.0001). FE significantly improved SPID, pain intensity difference, and pain relief compared with placebo from 6 to 60 minutes’ postadministration. Patients with BTP who received placebo required the use of rescue medication more often than those treated with FE (38.4% vs 17.5%; P < 0.0001). A significant improvement in pain scores (>33% and >50% reductions) was also reported for BTP treated with FE. Pain scores for patients with BTP with a neuropathic component (13 patients) were lower with FE than for those receiving placebo, but the difference was not significant. AEs were of mild or moderate severity and typical of opioid drugs.

Conclusions: This newly developed galenic formulation with a higher early systemic exposure and a shorter T_max compared with oral transmucosal fentanyl citrate makes FE a particularly suitable formulation for the management of BTP in opioid-treated cancer patients due to the very rapid onset of action. FE provided significant improvement in pain intensity of BTP compared with placebo as early as 6 minutes’ postadministration with a sustained effect over 60 minutes. FE was well tolerated by patients. Clinical Trials.gov identifier: NCT 01842893. (Clin Ther. 2014;36:333-343) © 2014 Elsevier HS Journals, Inc. All rights reserved.

Key words: breakthrough pain, cancer pain, fentanyl citrate, sublingual tablet.
INTRODUCTION
Approximately two-thirds of patients with advanced cancer report chronic pain requiring the use of strong opioids. Integrating effective and appropriate analgesia strategies that could improve the control of cancer pain is essential. However, even though background pain is well controlled, patients frequently experience acute exacerbation of their chronic pain, known as breakthrough pain (BTP). The characteristics of BTP are a rapid onset, a short duration (<30 minutes), and a severe intensity.

There is no gold standard treatment for managing BTP, but given the heterogeneous nature of the pain, several strategies, including pharmacologic and nonpharmacologic therapies, are used to relieve it. Among the pharmacologic treatments, the use of rescue doses of analgesics is the most commonly used strategy. The European Association for Palliative Care has recently published recommendations for the use of opioids for BTP: “episodes of BTP should be treated with immediate release oral opioids or with buccal or intranasal fentanyl preparations; these fentanyl preparations in some cases are preferable because of more rapid onset of action and shorter duration of effect.”

A number of oral transmucosal formulations are currently available: oral transmucosal fentanyl citrate (OTFC), a fentanyl buccal tablet (FBT), a sublingual orally disintegrating tablet, and fentanyl buccal soluble film. More recently, intranasal formulations have become available (intranasal fentanyl spray and fentanyl pectin nasal spray). Randomized controlled trials have demonstrated that all these formulations offer effective pain relief with a rapid onset of action (10–15 minutes) and a good tolerability.

Ethypharm (Saint Cloud, France) developed a new sublingual formulation of fentanyl citrate for the treatment of BTP in cancer patients with opioid background treatment. The product contains fentanyl citrate as the sole active ingredient. The sublingual tablet consists of different layers coated onto a neutral core; the fentanyl citrate layer is surrounded by an alkalinizing layer that increases the solubility of fentanyl and provides optimal oromucosal conditions for rapid dissolution and absorption. The pharmacokinetics of fentanyl Ethypharm (FE) were studied in healthy volunteers and compared with those of the reference product (OTFC). Bioequivalence was demonstrated with OTFC in a ratio of 1.5. The absolute bioavailability of FE was estimated to be ~70%. FE has a higher early exposure than OTFC, and this finding was also reflected by the shorter T_max.

Six strengths of FE were developed: 67, 133, 267, 400, 533, and 800 µg. Only the 5 higher dosages where used for the purpose of the present study.

The objective of the present study was to assess the efficacy and safety of FE when used to relieve BTP in opioid-treated cancer patients.

PATIENTS AND METHODS
Study Design
This was a prospective, multicenter, double-blind, placebo-controlled, randomized study comparing FE with placebo for the treatment of BTP in cancer patients experiencing 1 to 4 episodes of BTP per day despite treatment with around-the-clock opioids. The study consisted of 2 treatment periods: first, an open-label, escalating dose titration period to identify an optimal dose that would provide adequate pain relief for 2 consecutive episodes of BTP with an acceptable level of adverse events (AEs); and second, a randomized, double-blind, placebo-controlled, crossover period to assess the efficacy of FE.

The study was conducted at 21 centers managing cancer patients in the Czech Republic (ETHYFYL Study Group). The titration period and the double-blind period were conducted either at the hospital or patient’s home at the discretion of the investigator. The clinical trial was conducted in accordance with the ethical and scientific principles of the Declaration of Helsinki, the International Conference on Harmonisation Guideline for Good Clinical Practice (CPMP/ICH/135/95 January 1997), and the European Clinical Directive (2001/20/EC), as well as the applicable national law of the Czech Republic and its subsequent amendments.

Before initiating the study, the study protocol and its related documents (including the patient information and informed consent form) were submitted for approval to the Czech Multi-centric Ethics Committee, the local ethics committees of each site, and to the Czech Competent Authority. Each patient provided his or her written informed consent before study enrollment.
Patient Selection

Eligible patients were adult men or nonpregnant, nonlactating women, with a confirmed diagnosis of cancer, experiencing 1 to 4 episodes of BTP per day that were adequately controlled with a stable dose of standard rescue medication. Background pain intensity must have been stable for at least 1 week before study enrollment and scored as ≤4 on an 11-point numerical rating scale (NRS; 0 = no pain; 10 = worst pain). The opioid dosage regimen must have been stable for at least 1 week before study enrollment and was required to be 60 to 1000 mg of oral morphine daily or at least 25 μg/h of transdermal fentanyl or at least 30 mg of oxycodone or 8 mg of oral hydromorphone daily, or an equianalgesic dose of an alternative opioid. Other inclusion criteria were: an Eastern Cooperative Oncology Group performance status score ≤3, a life expectancy of at least 2 months, and the patient willing and able to comply with study procedures.

Patients with 1 of the following criteria were excluded from the study: primary-source BTP not cancer related; recent therapy (within 30 days) or planned therapy during the study that could alter pain or response to analgesics during the study such as palliative radiation therapy or a nerve block; hypersensitivity to fentanyl or any of the excipients; moderate or severe hepatic or renal impairment; risk of bradyarrhythmia because of underlying heart disease; sleep apnea or active brain metastases with increased intracranial pressure; severe chronic obstructive pulmonary disease or severe respiratory depression; recent history of substance abuse or neurologic or psychiatric impairment that could compromise study data collection; use of intrathecal opioids; previous or concomitant therapy with cytochrome P450 3A4 inhibitors, partial opioid agonists/antagonists, or monoamine oxidase inhibitors; and intake of an investigational new drug within 30 days before the first study drug administration.

Treatment Administration and Study Procedures

During the open-label period, patients were titrated to a dose that provided adequate pain relief for 2 consecutive episodes of BTP with an acceptable level of AEs. Five doses were used, ranging from an initial single dose of 133 μg to a maximum single dose of 800 μg. After administration of the initial dose, patients were closely monitored for 2 hours; if they experienced intolerable AEs, they discontinued the study. If adequate analgesia was not obtained within 15 to 30 minutes of administration of the starting dose, a second dose of 133 μg was administered. If adequate analgesia was not obtained within 15 to 30 minutes after this second dose, patients were allowed to take their usual rescue medication, and the next BTP episode was treated with the next dose; this cycle continued, until identification of the effective and optimal dose. No more than 2 doses were to be used to treat an individual BTP episode; if no adequate analgesia was obtained with the titrating dose of 267 or 400 μg, patients were allowed to take a second dose of 133 μg. Similarly, if no analgesia was obtained with 533 μg, the second dose had to be 267 μg. If the 800-μg dose was ineffective, or none of the previous tested doses provided satisfactory pain relief (rescue medication taken for all tested doses) or FE produced unacceptable AEs, patients were discontinued from the study.

Once the optimal dose had been established, patients were randomized into the double-blind crossover treatment period by using an Interactive Web Response System. During this double-blind period, patients were randomly assigned to 1 of the 13 prespecified dose sequences with 9 tablets: 6 tablets of FE at the optimal dose identified during the open-label period and 3 matching placebo tablets. Patients were instructed to use the tablets in a consecutive order for the occurrence of successive BTP episodes. If satisfactory pain relief was not achieved within 15 to 30 minutes of administration of the tablet, patients were allowed to use their usual rescue medication.

For both the open-label and the double-blind periods, a maximum of 4 episodes of BTP per day could be treated with study drugs with an interval of at least 2 hours between doses. Patients were instructed to place the tablet under the tongue until complete dissolution. If needed, remnants could be swallowed after 30 minutes. Patients experiencing dry mouth could drink some water to moisten the buccal mucosa before the tablet intake. Telephone contacts with the patients were conducted at least 3 times per week during the open-label titration period and the double-blind period to ensure that study procedures were being followed and any AE data were collected.
Efficacy and Safety Outcomes Measures

Patient diaries were used to collect data during the open-label titration and double-blind periods. Baseline pain intensity before treating an episode of BTP was recorded by using an 11-point NRS (0 = no pain; 10 = worst pain). Pain intensity and pain relief scores were then recorded after each dose intake at 3, 6, 10, 15, 30, and 60 minutes’ postdose. Pain relief was assessed by using a 5-point NRS (0 = none; 1 = slight; 2 = moderate; 3 = a lot; 4 = complete). Patients had to record any use of rescue medication throughout the study.

At the enrollment visit, the neuropathic component of BTP was assessed by using the French DN4 questionnaire (Douleur Neuropathique 4 questions/Neuropathic pain 4 questions). The total DN4 score was calculated by using the sum of the 10 items of the questionnaire according to the following rule: yes = 1, no = 0. A BTP episode was defined as having a neuropathic component if the total DN4 score was ≥4.

The primary efficacy end point was the sum of pain intensity differences 30 minutes after dosing (SPID30). The SPID30 was calculated for each BTP episode treated with the double-blind study medication taken by each patient, as the weighted sum of the pain intensity difference (PID) of all time points through 30 minutes’ postdose. Secondary efficacy end points included: SPID at 3, 6, 10, 15, and 60 minutes after study drug intake; SPID at 15 and 30 minutes according to the pathophysiology of the pain (with or without neuropathic component); PID and pain relief at 3, 6, 10, 15, 30, and 60 minutes’ postdose; the proportion of BTP episodes requiring rescue medication; and the proportion of BTP episodes with an improvement in pain intensity scores >33% and >50% at 15 and 30 minutes.

The safety profile was assessed by the investigators during the entire study period by recording AEs, vital signs measurements, and global physical examination. Concomitant medications were recorded throughout the study.

Statistical Analysis

Efficacy analysis was primarily performed on a modified intention-to-treat (mITT) population defined as all patients randomized to study who were treated with at least 1 dose of FE and 1 dose of matched placebo and who provided at least 1 baseline and postbaseline pain intensity score for each of the 2 doses. The following approach was used to input missing data before calculating the average values for each patient: the last-observation-carried-forward method and the baseline-observation-carried-forward method for missing pain intensity values due to rescue medication intake. A sensitivity analysis was performed on the per-protocol set, defined as all patients from the mITT set with no major protocol violations. The safety set was defined as all patients who received at least 1 dose of FE during the open-label titration period.

All statistical analyses were performed by using SAS version 9.2 (SAS Institute, Inc, Cary, North Carolina). For the primary end point, an ANCOVA model was used to compare the study treatments, with the SPID30 score as the dependent variable and treatment (FE or placebo) and pooled centers as covariates.

For the secondary efficacy end points, pain relief and PID were compared between the FE and placebo groups at each time point by using the 1-sample Wilcoxon signed rank test. The proportion of episodes of BTP that required rescue medication and the proportion of episodes of BTP with >33% and >50% improvement in pain intensity scores at 15 and 30 minutes were compared between the FE and placebo groups by using generalized estimating equations. Descriptive statistics were used for the description of the study population, baseline characteristics, and safety parameters.

The sample size was calculated assuming an effect size of 0.4 (mean difference divided by the SD of the difference) for the SPID30 difference between FE and placebo. To provide a power of 90% to detect an effect size of 0.4 for the treatment difference between both groups, 68 evaluable patients for the primary efficacy end point were required using a 1-sample \( t \) test with a 2-sided type I error of 5%. Anticipating an early discontinuation rate of 50%, 136 patients had to be enrolled.

RESULTS

Patient Disposition and Baseline Demographic Characteristics

A total of 93 patients were enrolled and 91 were included in the open-label titration period and in the safety population (Figure 1). Of the 91 patients enrolled in the open-label period, 13 (14.3%)
discontinued the study. The most common reasons for discontinuation were noncompliance with titration procedure \( (n = 4) \) and nonrespect of randomization criteria \( (n = 4) \). Only 1 patient discontinued the study due to an AE (vomiting). Of the 78 patients randomized to the double-blind period, 2 patients did not receive any study medication. Three patients were excluded from the mITT population because it was not possible to check the accuracy of the patient diary data.

Demographic and baseline characteristics of the study population are provided in the Table. There were no major differences between the safety and the mITT populations. In the safety population, the most common background opioid medications were fentanyl (78%), hydromorphone (11%), and oxycodone (8.8%). Thirteen patients (17.8%) reported a neuropathic component of their BTP in the mITT population.

**Dosing**

During the open-label titration period, patients were treated for a mean (SD) of 3.4 (1.5) BTP episodes. For the 78 patients who entered the double-blind period, the effective dose identified was 133 μg for 28 patients (35.9%), 267 μg for 24 patients (30.8%), 400 μg for 11 patients (14.1%), 533 μg for 10 patients (12.8%), and 800 μg for 5 patients (6.4%) (Figure 2). The mean duration of exposure to study drug was 2.8 days in the titration period, 6.2 days in the double-blind period, and 8.2 days for the whole study.

**Efficacy**

A total of 436 BTP episodes were treated with FE and 218 with placebo. The mean (SD) pain intensity score of BTP episodes was similar before the use of FE and the use of placebo (7.0 [1.4]).
SPID30 was significantly greater for patients with BTP episodes treated with FE compared with those receiving placebo. The mean SPID30 was 75.0 (49.8) for FE and 52.5 (52.8) for placebo ($P < 0.0001$). After adjustment for the treatment in the mixed covariance model, a statistically significant treatment effect in favor of FE was also reported, with a mean treatment difference of 22.3 (least squares means, 75.0 [95% CI: 68.2–81.7] for FE and 52.7 [95% CI, 44.7–60.6] for placebo).

The mean SPID scores were significantly higher for FE compared with placebo at each time point, from 6 minutes’ ($P = 0.02$) to 60 minutes’ ($P < 0.0001$) postdose (Figure 3). Consistent with the SPID results, the differences between the patients’ PID and pain relief of BTP episodes treated with FE and those receiving placebo were statistically significant in favor of FE, starting at 6 minutes’ postdose and continuing until the last assessment at 60 minutes ($P < 0.0001$) (Figures 4 and 5). For the 13 patients experiencing a neuropathic component of their BTP, SPID at 15 and 30 minutes were higher for the BTP episodes treated with FE compared with those managed with placebo, but the differences were not statistically significant ($P = 0.07$). The percentage of BTP episodes with $>33\%$ and $>50\%$ reduction in

### Table. Baseline demographic characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Safety Population (n = 91)</th>
<th>mITT Population (n = 73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>64.5 (11.9)</td>
<td>64.7 (11.8)</td>
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<tr>
<td>Male sex, no. (%)</td>
<td>50 (54.9)</td>
<td>41 (56.2)</td>
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<tr>
<td>Weight, mean (SD), kg</td>
<td>70.0 (14.4)</td>
<td>70.6 (14.7)</td>
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<tr>
<td>ECOG performance status, no. (%)</td>
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<td></td>
</tr>
<tr>
<td>1</td>
<td>19 (20.9)</td>
<td>14 (19.2)</td>
</tr>
<tr>
<td>2</td>
<td>61 (67.0)</td>
<td>48 (65.8)</td>
</tr>
<tr>
<td>3</td>
<td>11 (12.1)</td>
<td>11 (15.1)</td>
</tr>
<tr>
<td>Primary tumor type, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urogenital cancer</td>
<td>29 (31.9)</td>
<td>25 (34.2)</td>
</tr>
<tr>
<td>Digestive cancer</td>
<td>24 (26.3)</td>
<td>20 (27.4)</td>
</tr>
<tr>
<td>Head and neck cancer</td>
<td>15 (16.5)</td>
<td>11 (15.1)</td>
</tr>
<tr>
<td>Lung and lower aerodigestive tract cancer</td>
<td>9 (9.9)</td>
<td>6 (8.2)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>8 (8.8)</td>
<td>6 (8.2)</td>
</tr>
<tr>
<td>Hematologic malignancies</td>
<td>2 (2.2)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (4.4)</td>
<td>4 (5.5)</td>
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<tr>
<td>Time since diagnosis of cancer, mean (SD), y</td>
<td>3.3 (3.9)</td>
<td>3.0 (3.3)</td>
</tr>
<tr>
<td>Mean (SD) no. of episodes of BTP per day</td>
<td>2.2 (0.8)</td>
<td>2.1 (0.8)</td>
</tr>
<tr>
<td>Background pain intensity (NRS score 0–10), mean (SD)</td>
<td>3.2 (0.7)</td>
<td>3.2 (0.7)</td>
</tr>
<tr>
<td>Background opioid medications, no. (%)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>71 (78.0)</td>
<td>54 (74.0)</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>10 (11.0)</td>
<td>10 (13.7)</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>8 (8.8)</td>
<td>7 (9.6)</td>
</tr>
<tr>
<td>Morphine</td>
<td>4 (4.4)</td>
<td>4 (5.5)</td>
</tr>
<tr>
<td>Other</td>
<td>7 (7.7)</td>
<td>6 (8.2)</td>
</tr>
<tr>
<td>Neuropathic component of pain, no. (%)</td>
<td>16 (17.6)</td>
<td>13 (17.8)</td>
</tr>
</tbody>
</table>

mITT = modified intention-to-treat; ECOG = Eastern Cooperative Oncology Group; BTP = breakthrough pain; NRS = numerical rating scale.

*Patients may have reported $>1$ drug for background opioid medication.
pain scores was significantly greater with FE than with placebo. At 15 minutes, 58.4% of BTP episodes treated with FE and 38.4% of those managed with placebo had a >33% reduction in pain scores \( (P < 0.0001) \). At 30 minutes, these percentages were increased to 71.9% and 50.5%, respectively \( (P < 0.0001) \). A >50% reduction in pain scores was observed for 26.7% of BTP episodes at 15 minutes in the FE group and for 19% in the placebo group \( (P = 0.02) \); at 30 minutes, the difference was also statistically significant between FE (53.3% of BTP episodes) and placebo (36.1% of BTP episodes) \( (P = 0.0004) \).

Rescue medication was used in 38.4% of patients with BTP episodes receiving placebo compared with 17.5% of those treated with FE \( (P < 0.0001) \).

Safety

During the whole study period, 77 treatment-emergent AEs (TEAEs) were reported by 25 patients (27.5%). The most common TEAEs were typical of opioid administration and included vomiting (5.5%), nausea (4.4%), diarrhea (3.3%), dry mouth (3.3%), and somnolence (2.2%). Most of the TEAEs were of mild or moderate severity. Forty of these TEAEs, reported by 8.8% of the patients, were considered by the investigators to be related to study treatment. Two patients experienced TEAEs leading to premature discontinuation of the study: 1 with mild

Figure 2. Optimal dose identified during the open-label titration period among the 78 patients who entered the double-blind period of the study.

Figure 3. Evolution of sum of pain intensity differences (SPID) scores (mean [SE]) over time in the modified intention-to-treat population \( (n = 73) \). The mean SPID scores were significantly higher for fentanyl Ethypharm (FE) compared with placebo at each time point from 6 \( (P = 0.02) \) to 60 \( (P < 0.0001) \) minutes’ postdose. Error bars indicate SEs.
vomiting during the open-label titration period and 1 with deep somnolence for which the patient had to be hospitalized. This was the only serious AE of the study and was considered by the investigator to be unrelated to study treatment. Only 3 patients experienced dry mouth (all during the titration period); 2 of the patient episodes were considered by the investigator to be study drug related. No other oral AEs were reported in the study.

**DISCUSSION**

BTP is common in patients with cancer pain, and it is characterized by a transient exacerbation of pain, despite a stable and adequately controlled background pain.\(^3\)–\(^7\) The use of rescue medication is the most common pharmacologic treatment for the management of BTP. Drugs with a rapid onset of action, a relatively short duration of action, and minimal adverse effects are the most adopted treatment.\(^1,8\) Despite recent European recommendations\(^1\) in their favor, and demonstration of their clinical effectiveness and good tolerability,\(^9\)–\(^17\) transmucosal fentanyl formulations are not yet widely used. A recent study has characterized BTP in a European population of cancer patients and determined patient opinion about their current treatment of BTP.\(^19\) Not surprisingly, the median time to peak intensity was 15 minutes, pain was reported as severe by 60% of patients, and interference with daily activities was noted as a consequence. Most patients (76%) identified an intervention that usually improved BTP; the interventions that were successful were pharmacologic, nonpharmacologic, or a combination of both; the rescue medication was always an opioid, more or less associated with a nonopioid drug and/or a nonpharmacologic intervention; and only a minority of patients (9%) received 1 licensed transmucosal fentanyl formulation. Patients often report issues related to the efficacy and/or tolerability of their rescue medication, and the authors emphasize that transmucosal opioid drugs may address some of these issues.

The present study achieved its primary efficacy endpoint by demonstrating the clinical effectiveness of FE in the management of BTP episodes in opioid-treated patients.
cancer patients, as evidenced by a statistically significant difference of SPID30 in favor of FE compared with placebo ($P < 0.0001$). Furthermore, SPID, PID, and pain relief scores were significantly greater than placebo starting 6 minutes after study drug administration and continuing through 60 minutes. FE was also superior to placebo for the reduction of pain scores $\geq 33\%$ and $\geq 50\%$ at 15 and 30 minutes, and patients required significantly more rescue medication for BTP episodes managed with placebo than for episodes treated with FE ($P < 0.0001$). SPID scores for BTP episodes with a neuropathic component were higher for FE compared with placebo, but the differences did not reach statistical significance, probably because of the low number of patients involved ($n = 13$). Consequently, no conclusion can be drawn regarding the efficacy of FE on pain relief of BTP with a neuropathic component, and this finding thus requires further investigation.

On the basis of a high dropout rate (30%–50% of patients) after enrollment reported in clinical trials with different fentanyl formulations, $^9,^11–^14,^16$ we had anticipated a 50% dropout during the open-label period. Premature withdrawals are usually mainly due to AEs, lack of efficacy, and protocol deviations/noncompliance with study procedures. In our study, only 13 patients (14.3%) were withdrawn during the open-label titration period, and 85.7% of patients identified an effective dose. Only 1 patient was withdrawn because of an AE (vomiting) and 1 due to lack of efficacy; other reasons were mainly due to nonrespect of study procedures/inclusion criteria.

Another important difference we found compared with other oromucosal formulations is the distribution of effective doses: 66.7% of patients used the 2 lowest doses (133 and 267 $\mu$g). For OTFC studies, other authors have reported use of the 2 lowest doses (200 and 400 $\mu$g) in 29% $^{11}$ and 38%, $^{20}$ respectively, of patients. For FBT, Portenoy et al. $^{12}$ reported that 16% of enrolled patients discontinued the study because of lack of efficacy at the highest tolerated dose and that the 2 lowest dosages (100 and 200 $\mu$g) were identified as effective doses for 30% of the patients. In the study by Slatkin et al. $^{13}$ only 20% of patients used the 2

Figure 5. Evolution of pain relief scores (mean [SE]) over time in the modified intention-to-treat population ($n = 73$). The mean pain relief scores were significantly higher for fentanyl Ethypharm (FE) compared with placebo at each time point from 6 ($P = 0.002$) to 60 ($P < 0.0001$) minutes’ postdose. Pain relief scores: $0 =$ no relief; $1 =$ slight relief; $2 =$ moderate relief; $3 =$ a lot of relief; and $4 =$ complete relief. Error bars indicate SEs.
lowest doses of FBT. This percentage was reported to be 17% for fentanyl orally disintegrating tablet\textsuperscript{14} and 23.4% for fentanyl buccal soluble film\textsuperscript{16}.

FE provided significant pain relief for BTP episodes as early as 6 minutes after drug administration in the present study. A rapid onset of action was expected based on the specific new galenic formulation of FE and pharmacokinetic results showing a higher early systemic exposure and a shorter $T_{\text{max}}$ compared with OTFC. This is the shortest onset of action reported with an oral transmucosal fentanyl formulation in this patient population. The very rapid onset of action could explain the use of lower doses of FE to relieve BTP. Nevertheless, the present study was not a direct comparative one, and no conclusions can be drawn regarding the efficacy of FE compared with other oral transmucosal fentanyl formulations.

Overall, FE was well tolerated in this selected population of opioid-treated cancer patients. Few AEs were reported, and all were typical of opioid drugs. No symptoms of respiratory depression were observed. Only 1 serious AE occurred during the study, and it was considered by the investigator to be unrelated to the study medication. All these results make FE a particularly suitable formulation for the management of BTP episodes in opioid-treated cancer patients.

CONCLUSIONS

The study showed the effectiveness and the good safety profile of FE in the management of BTP episodes in opioid-treated cancer patients. The new galenic formulation of FE may have an advantage over the currently available oral transmucosal fentanyl formulations in terms of onset of action.

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CONFLICTS OF INTEREST

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Dr. Trinquet is an employee of Ethypharm. Dr. Bullier is an employee of ICTA PM, the contract research organization that received fees from Ethypharm to conduct the study. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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Address correspondence to: Françoise Trinquet, MD, Ethypharm, 194 Bureaux de la Colline, 92213 Saint Cloud Cedex, France. E-mail: trinquet.francoise@ethypharm.com