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ORIGINAL ARTICLE

Improved patient functioning after treatment of breakthrough cancer pain: an open-label study of fentanyl buccal tablet in patients with cancer pain

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Abstract
Purpose This open-label study evaluated the effects of fentanyl buccal tablet (FBT) on functioning and mood in cancer patients with breakthrough cancer pain (BTcP).
Methods Opioid-tolerant patients in seven European countries with up to four BTcP episodes/day received FBT doses (100–800 μg) identified during open-label titration to treat up to eight BTcP episodes during an open-label treatment period. In countries where FBT was not commercially available, patients could enter an open-label continuation phase. Functionality and satisfaction assessments included change from baseline to the end of the treatment period in the modified Brief Pain Inventory (BPI-7S) seven-item interference subscale, patient's global assessment of satisfaction and ease of use, and Patient's Global Impression of Change (PGIC). Safety was also assessed.
Results Of 330 randomized patients, 218 completed the treatment period and 88 entered the continuation phase. Median background pain intensity was 4.0 (mild) throughout the study. After the treatment period, mean (SD) global modified BPI-7S score improved from 39.7 (15.9) at baseline to 31.6 (16.8) for a mean change of −8.6 (95 % confidence interval CI −10.5, −6.7; $P<0.0001$), and 74.5 % of patients reported improvement in overall status (PGIC) compared with 25.5 % who reported no change or worsening ($P<0.001$). Treatment-related adverse events (≥2 patients) during the continuation phase were application site erythema (6.9 %), application site swelling (4.6 %), and vertigo (4.6 %).
Conclusions FBT may improve patient functioning, mood, and overall satisfaction in the management of BTcP. Long-term data did not indicate new safety concerns with FBT doses up to 800 μg.

This study was previously presented at (1) The 15th World Congress of Pain Clinicians (WSPC); June 27-30, 2012; Granada, Spain; (2) The International Association for the Study of Pain's (IASP) 14th World Congress on Pain; August 27-31, 2012; Milan, Italy; and (3) The European Society for Medical Oncology (ESMO) 2012 Congress; September 28-October 2, 2012; Vienna, Austria.

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Keywords Breakthrough pain · Chronic pain · Fentanyl buccal tablet · Opioid analgesic · Pain management · Cancer patients

Introduction

Cancer patients with chronic pain controlled by maintenance analgesics commonly experience breakthrough cancer pain (BTcP), defined as a transitory exacerbation of pain occurring in the presence of otherwise controlled, background pain [1]. The prevalence of BTcP among patients with controlled, background chronic cancer pain ranges from 33 to 89 %, depending on clinical setting [1–6], how BTcP was defined [6–8], differences in BTcP diagnostic criteria, and inclusion of patients with poorly controlled background pain [4, 6]. Cancer patients with BTcP may experience substantial impairments in physical (e.g., walking, sleeping), psychological (e.g., anxiety, depression), and social (e.g., work, relationships) functioning compared with those with controlled, background chronic cancer pain without BTcP [2, 9, 10]. Not surprisingly, BTcP negatively affects quality of life (QOL) [9] and satisfaction with pain management [4]. Thus, effective management of BTcP has the potential to improve functional status and QOL in relevant patients with chronic cancer pain.

Fentanyl buccal tablet (FBT; Effentora®, Fentora®, Teva Pharmaceuticals Industries Ltd., Petah Tikva, Israel) is a rapid-onset opioid indicated for the management of BTcP in adults with cancer who are "opioid tolerant" [11, 12]. FBT was shown to reduce BTcP intensity and was generally well tolerated in opioid-tolerant patients with cancer-related chronic pain in two double-blind, randomized, placebo-controlled studies [13, 14] and a long-term, open-label safety study [15].

A pan-European, multicenter, phase 3b/4 clinical study in patients with BTcP was conducted to evaluate dose titration of FBT starting with 100 vs. 200 μg. Non-inferiority was established with the percentage of patients achieving an effective dose starting titration at 200 μg (81.4 %) compared with the 100-μg (75.2 %) starting dose. Primary results from this study have been reported elsewhere [16]. In this report, we present the effects of FBT on patients' functional status and mood, as well as the long-term safety of FBT from the aforementioned study.

Patients and methods

Study design

This open-label, randomized, dose-titration, non-inferiority study was conducted at 135 centers in France, Germany, Spain, Ireland, Italy, Poland, and the UK (EudractCT number 2008-001841-24). The study was conducted in full accordance with the Good Clinical Practice: Consolidated Guideline approved by the International Conference on Harmonisation [17] and applicable national and local laws and regulations. The protocol was approved by the institutional review boards, and written informed consent was obtained from patients before screening.

Detailed methods, eligibility criteria, and primary efficacy results from this study have been previously published [16]. Men and women ≥18 years of age with histologically documented cancer and stable background pain due to cancer who were experiencing an average of up to four BTcP episodes per 24 h were enrolled. All patients had used oral morphine ≥60 mg/day, transdermal fentanyl ≥25 μg/h, oxycodone ≥30 mg/day, hydromorphone ≥8 mg/day, or an equianalgesic dose of another opioid as maintenance therapy for their background pain for at least 1 week before enrollment. Patients were excluded if they had uncontrolled or rapidly escalating pain, respiratory depression, or chronic obstructive pulmonary disease.

The study consisted of a screening phase, randomized dose titration period, treatment period, and continuation phase. After screening, enrolled patients were randomized 1:1 to receive FBT 100 or 200 μg as a starting dose. Patients self-administered FBT and titrated to an effective dose (100, 200, 400, 600, or 800 μg) that provided adequate analgesia and minimized undesirable effects within the first 30 min of administration for two consecutive episodes of BTcP. Patients then entered an 8-day treatment period during which they treated up to eight BTcP episodes with the effective FBT dose identified during the titration period.

Patients completing the open-label treatment period in countries where FBT was not commercially available (France, Italy, Poland, and Spain) had the option of entering an open-label continuation phase after visit 4. During the continuation phase, patients were supplied with FBT at their effective dose for 4 weeks. Patients were instructed to wait at least 4 h before treating another BTcP episode with FBT. If another episode occurred within 4 h, patients were permitted to use their usual supplemental medication. Patients were required to return to the study site every 4 weeks for safety assessments. The continuation phase ended when FBT became commercially available in the country.

Assessments

Cancer history, background cancer pain, and BTcP characteristics

At screening, investigators recorded cancer site, time since diagnosis, extent of disease, and treatment received for primary and secondary solid tumor and/or hematologic malignancy.

Background cancer pain and BTcP were evaluated at screening. Evaluation included anatomic location(s), etiology

of pain, and time since onset. Patients rated average overall background pain intensity during the preceding week using an 11-point numeric rating scale (0=no pain and 10=pain as bad as you can imagine), as well as current medication(s). Patients also assessed background pain every evening during each of the three study periods (screening, titration, and treatment) and recorded their assessments in patient diaries.

Patients described episodes of BTcP in terms of average daily frequency, time from onset to peak intensity (without any treatment), duration, and need for medication. The average daily frequency of BTcP episodes was also assessed at enrollment using patient diary entries.

Modified BPI-7S questionnaire

Patients rated the impact of BTcP on their functional status at baseline and after the treatment period using the seven-item interference subscale of the modified Brief Pain Inventory-Short Form (BPI-7S) adapted to specifically assess BTcP. This subscale measures pain interference with general activity, mood, walking ability, normal work, relationships with others, sleep, and enjoyment of life on a 0- to 10-point numeric scale (0=does not interfere and 10=completely interferes). These ratings are summed to create a global score to indicate pain interference with overall function [18].

Patient's global assessment of satisfaction

Patients completed a Global Assessment of Satisfaction at baseline and after the treatment period. The patient's global assessment of satisfaction with treatment included eight questions related to medication performance and safety and ease and comfort of use [19]. Patients responded to questions using a five-point numeric scale (0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, and 4=very much).

Patient's global assessment of ease of use

Patients rated ease and convenience of FBT use after the treatment period by responding to the question, "Did you find this treatment easy/convenient to use for treatment of your BTcP episodes?" using a four-point numeric scale (0=poor, 1=fair, 2=easy, and 3=very easy).

Patient's Global Impression of Change (PGIC)

Patients rated overall status after the treatment period by responding to the question, "Since the start of the study my overall status is…?" using a seven-point scale (1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, and 7=very much worse) [20].

Safety

Safety during the continuation phase was assessed by evaluating reported adverse events (AEs), including withdrawal from the study because of AEs, serious AEs, and oral mucosal examination findings. AEs were also assessed according to type of opioid maintenance therapy (fentanyl based vs. other opioid). All AEs were coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA) terminology, version 13.0.

Statistical analysis

Data collected for cancer history, background cancer pain characteristics, and BTcP characteristics were summarized using descriptive statistics. Change from baseline to the end of the treatment period in interference subscale and global scores on the modified BPI-7S questionnaire were calculated, as well 95 % confidence intervals (CIs) for global scores. The mean change in global score was calculated by summing the mean changes in subscale scores for each patient. The number and percentage of patients recording each response for each question on the patient's global assessment of satisfaction were calculated for baseline and the end of the treatment period; the number and percentage of patients recording each response on the patient's global assessment of ease of use and the PGIC were calculated for the end of the treatment period. All patients who took at least one dose of FBT during the dose titration period and recorded a response on the relevant questionnaires were included in these analyses.

All randomized patients who took at least one dose of study medication during the continuation phase were included in the safety analyses. AEs were summarized separately for each study period by frequency, intensity, and relationship to study drug; serious or otherwise significant AEs were also noted. Analyses were performed using SAS® version 9.2 (SAS Institute, Cary, NC).

Post hoc statistical analyses

A series of unplanned post hoc analyses were performed to determine whether the observed effects of FBT on assessments of QOL and patient satisfaction were statistically significant. For modified BPI-7S and the patient's global assessment of satisfaction scores, paired *t*-tests were used to compare change from baseline (visit 2) to final visit. For PGIC, patients were categorized as "improved" (scores of 1–3 indicating at least minimal improvement) or "not Improved" (scores of 4–7 indicating no change or worsening) at the final visit. The number of patients in each category was compared using the binomial test. For the paired data, only observed data were used. For the PGIC, patients with missing responses

were counted as nonresponders. All analyses were two-sided, and $P \leq 0.05$ was the threshold for significance.

Results

Of the 442 patients screened, 330 were randomized, 281 entered the treatment period, 223 received at least one dose of FBT in the treatment period, and 218 completed the treatment period (Fig. 1). Of the 88 patients eligible for the open-label continuation phase, 87 (99 %) received at least one dose of study medication and were evaluated for safety in the continuation phase. The median duration of treatment with FBT during the continuation phase was 115 days (mean 204.2 days; range 1–684 days).

Patients had a mean (SD) age of 59.8 years (11.3) and mean (SD) body mass index of 24.6 kg/m^2 (4.9).

Baseline cancer characteristics are summarized in Table 1. Median time since first background cancer pain was 8.3 months. Etiology of background cancer pain was cancer in the majority of patients (85.5 %) and a result of treatment of malignancy in 11.8 % of patients. Background cancer pain was located most frequently in the back (31.8 %), abdomen (20.3 %), and chest (19.7 %). Background pain intensity was stable throughout the study, with median scores of 4.0 across the screening, titration, and treatment periods. All patients were receiving opioid maintenance therapy. The most common opioid pain medications taken by patients were transdermal fentanyl (n=151; 45.8 %), oral morphine (n=75; 22.7 %), oral oxycodone (n=62; 18.8 %), and oral hydromorphone (n=22; 6.7 %); a patient could have been counted more than once if they were using combination therapy.

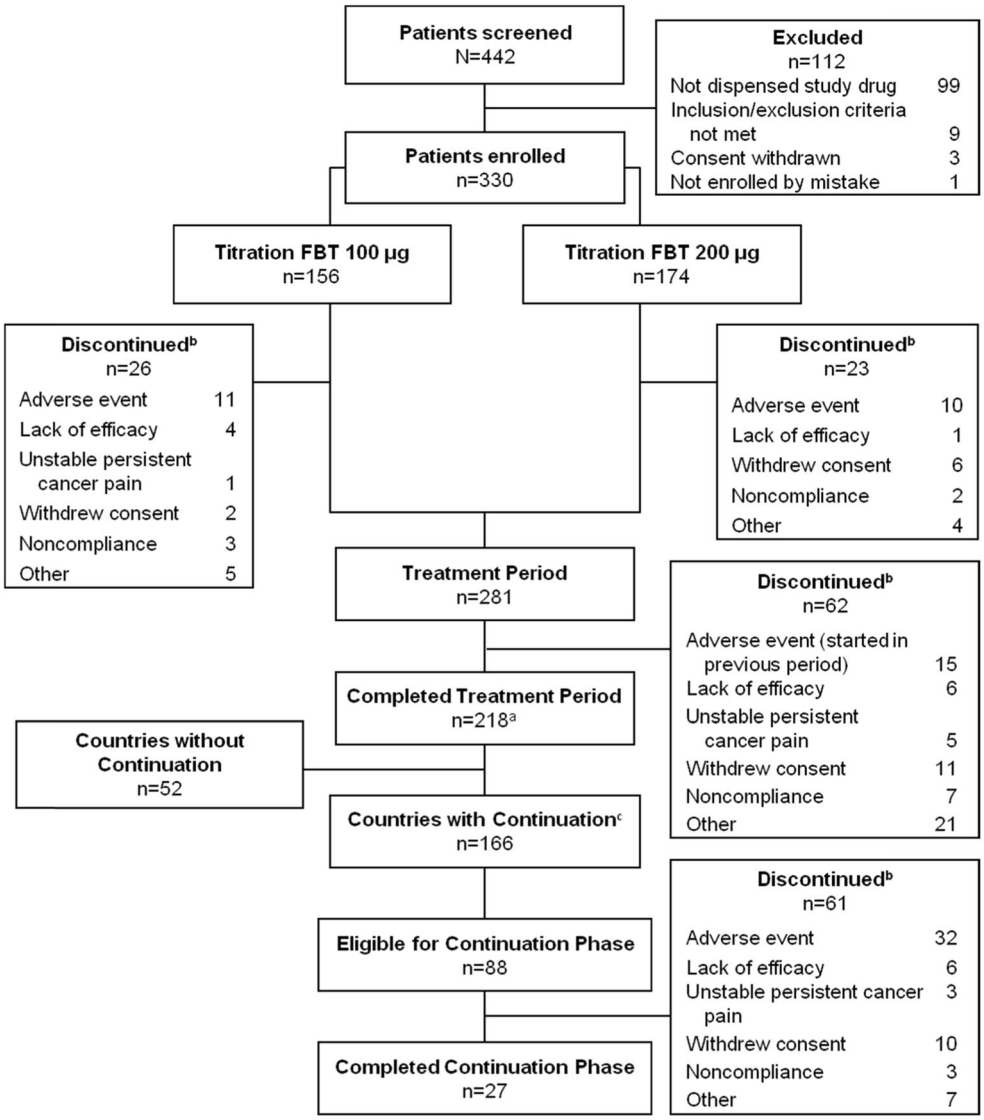

Fig. 1 Patient disposition. [a]One patient was not included in the total number of patients who completed the study as a result of a discrepancy in the data recorded at visit 4 (final visit). [b]Patients may have had more than one reason for discontinuing the study. [c]FBT was not available after visit 4 at sites in France, Italy, Poland, and Spain

Table 1 Baseline cancer characteristics

Characteristic	Total (*N*=330)
Site of primary malignancy, *n* (%)	
Breast	67 (20.3)
Lung	47 (14.2)
Colon/rectum	40 (12.1)
Prostate	25 (7.6)
Head/neck	24 (7.3)
Pancreas/stomach	24 (7.3)
Myeloma	9 (2.7)
Esophageal	6 (1.8)
Leukemia/lymphoma	6 (1.8)
Other	82 (24.8)
Extent of disease, *n* (%)	
Local	134 (40.6)
Metastatic	
Bone	151 (45.8)
Liver	69 (20.9)
Lung	65 (19.7)
Other	93 (28.2)
Ongoing cancer treatments, *n* (%)[a]	
Chemotherapy	87 (26.7)
Hormonal therapy	32 (9.8)
Radiotherapy	13 (4.0)
Other	10 (3.1)

[a] Percentages are of patients providing information about treatments received (*n*=326)

The median time since first episode of BTcP was 4.8 months (range 0–230.8 months). The relationship of BTcP to persistent cancer pain was most frequently reported as flare-up of persistent cancer pain (80.9 %), the physiology as mixed (53.3 %), and the type of BTcP as spontaneous (66.2 %). The average daily frequency of BTcP was two to three episodes for 64.2 % of patients. The average time from onset to peak intensity (without any treatment) was up to 30 min for 79.4 % of patients, and the average duration of BTcP episodes (without any treatment) was reported as >30 min for 47.3 % of patients, 10 to 30 min for 33 % of patients, and 0 to 10 min for 3.9 % of patients; the average duration was unknown in 15.8 % of patients. Most patients (93.6 %) took medication to treat BTcP at baseline. The most commonly used analgesics prior to study initiation included morphine (26.7 %) and fentanyl (17.8 %).

Results for the primary efficacy measure have been reported elsewhere [16]. A total of 245 patients (78.5 %) reached an effective dose after titration; the most frequent effective doses of FBT, as assessed by investigator, were 200 μg (39.6 % of patients) and 400 μg (26.9 % of patients).

Assessments

Modified BPI-7S questionnaire

Mean scores on all seven items of the interference subscale of the modified BPI-7S (general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life) were significantly decreased from baseline to the end of treatment period (all $P<0.0001$) (Fig. 2). The largest improvement was seen for enjoyment of life (mean change -1.5), and the smallest improvement was seen for walking ability (mean change −0.9). Mean global score for the modified BPI-7S decreased from 39.7 (95 % CI 37.5, 41.8; *n*=210) at baseline to 31.6 (95 % CI 29.3, 33.8; *n*=206) at the end of the treatment period (mean decrease −8.6; 95 % CI −10.5, −6.7; $P<0.0001$), indicating a statistically significant improvement in patients' functional status after treatment with FBT.

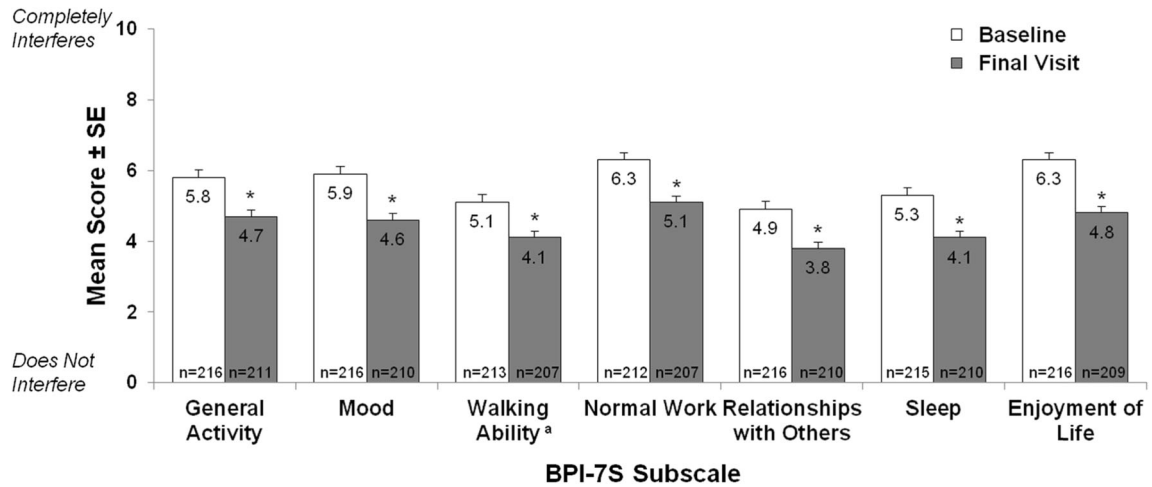

Fig. 2 Mean (SE) modified BPI-7S scores at baseline and the end of the treatment period. BPI-7S=seven-item interference subscale of the modified Brief Pain Inventory. *$P<0.0001$ vs. baseline, based on a paired *t*-test. [a]Values for baseline and final visit were determined by rounding, and change between values before rounding is −0.9353

Patient's global assessment of satisfaction and ease of use

Patient satisfaction was significantly improved after treatment with FBT, based on six of eight items on the patient's Global assessment of satisfaction (Fig. 3). Changes from baseline indicated statistically significant improvements with FBT vs. baseline BTcP treatment on the items patient-reported satisfaction with medication safety, comfort with use in public, quick relief of pain allowing the patient to sleep, adequate relief, ability to work fast, and overall satisfaction with FBT compared with prior BTcP medication (each $P<0.0001$) (Fig. 3). Likewise, the majority (83.3 %) of patients at the end of the treatment period responded that FBT was "very easy" (32.1 %) or "easy" (51.2 %) to use when asked, "Did you find this treatment easy/convenient to use for treatment through your BTcP episodes?" Only 3.3 % of patients reported that the ease/convenience of use was "poor" for FBT.

PGIC

Responses to the PGIC showed that 155 out of 208 patients (74.5 %) considered their overall status to have improved from baseline at the end of the treatment period vs. 53 (25.5 %) who reported no change or worsening ($P<0.001$).

Safety and tolerability of FBT

Safety data from the titration and treatment periods have been previously reported [16] and did not show any major concerns for the use of FBT at doses up to 800 μg. Nausea, vomiting, somnolence, and dizziness were the most frequent treatment-related AEs in the titration period, and application site erythema and application site swelling were the most frequent treatment-related AEs in the treatment period.

Patients included in the continuation safety analysis ($n=87$) had received FBT treatment for a median of 115.0 days. During the continuation phase, treatment-related AEs considered by the investigator to be possibly, probably, or definitely related to study medication were reported for 14 patients (16.1 %). The most common treatment-related AEs included application site erythema (6.9 %), application site swelling (4.6 %), and vertigo (4.6 %) (Table 2). The percentage of patients with abnormal oral mucosal findings was low throughout the continuation phase (generally ≤5 % patients at each visit).

The majority of serious AEs in the continuation phase were considered by the investigator to be related to underlying disease. Serious AEs were reported in 37 (42.5 %) patients (Table 2). Among the serious AEs, fatal outcomes were reported for 29 (78.4 %) patients. The primary cause of death in the continuation phase was malignant neoplasm progression ($n=15$). A total of 25 (28.7 %) patients had an AE leading to withdrawal from the continuation phase of the study; the most common AE leading to withdrawal was malignant neoplasm progression and/or development of new cancer in 12 patients (13.8 %).

Discussion

Findings from the present pan-European, multicenter study indicate that in opioid-tolerant cancer patients with well-controlled background pain, open-label treatment of BTcP

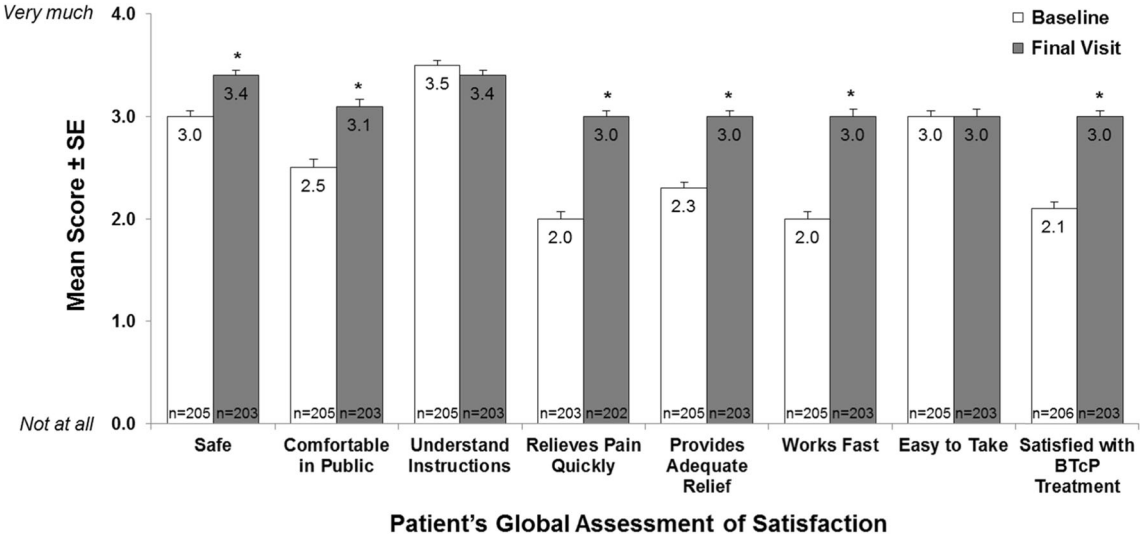

Fig. 3 Mean (SE) scores on patient's global assessment of satisfaction with breakthrough pain medication at baseline and with fentanyl buccal tablet at the end of the treatment period. Values reflect scores at baseline (with previous BTcP medication) and at the final visit (with FBT). Responses were made on a five-point numeric scale (0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, and 4=very much). *BTcP* breakthrough cancer pain. *$P<0.0001$ vs. baseline, based on a paired *t*-test

Table 2 Treatment-related and serious adverse events reported in ≥2 patients administering fentanyl buccal tablet in the continuation phase

No. of patients (%)	Continuation phase (n=87)
Patients with ≥1 treatment-related adverse event	14 (16.1)
Application site erythema	6 (6.9)
Application site swelling	4 (4.6)
Vertigo	4 (4.6)
Nausea	2 (2.3)
Somnolence	2 (2.3)
Constipation	2 (2.3)
Patients with ≥1 serious adverse event	37 (42.5)
Malignant neoplasm progression	15 (17.2)
New malignant neoplasm or metastases	8 (9.2)
Anemia	3 (3.4)
Dyspnea	3 (3.4)
Vomiting	3 (3.4)
Ileus	2 (2.3)
Pyrexia	2 (2.3)
Urinary tract infection	2 (2.3)
Back pain	2 (2.3)
Renal failure	2 (2.3)

episodes with FBT (100 to 800 μg) significantly decreased interference of BTcP in daily function; at the end of the 4-week open-label treatment period, significant improvements in global and subscale scores of the modified BPI-7S questionnaire were observed, with the greatest improvement reported for enjoyment of life. At the end of the 4-week treatment period, most patients indicated they were satisfied with FBT treatment of BTcP and most reported an improvement in overall status.

The majority of patients in the present investigation reported experiencing two to three BTcP episodes per day at screening. This level of BTcP had a significant negative effect on daily functioning and QOL based on responses on the modified BPI-7S. Patients at baseline reported that BTcP interfered the most with normal work, enjoyment of life, mood, and general activity. This is consistent with previous findings in patients [2, 9]. In these studies, scores on the BPI-7S demonstrated that patients with cancer and BTcP had significant impairment across all domains of functioning compared with patients with cancer and no BTcP, with the greatest effect on normal work, mood, and general activity. Similarly, broad impairments in functioning and QOL due to breakthrough pain have been described based on BPI scores in patients with noncancer chronic pain [19]. Such findings underscore the need for improving the management of BTcP.

After treatment with FBT for BTcP in the present study, the mean modified BPI-7S global score decreased significantly (i.e., improved) by −8.6 points from baseline to the end of the treatment period, with statistically significant decreases seen in all scores on the interference subscale. The greatest relative improvement from baseline was reported for enjoyment of life (−1.5 points); other subscales that showed improvements of a generally similar magnitude were mood (−1.4), sleep (−1.4), and normal work (−1.3). These findings suggest that managing BTcP episodes with FBT can reduce the negative effects of BTcP on physical, psychological, and social functioning. Similar improvements in QOL have been observed in clinical studies of other rapid-onset opioids [19, 21–23]. The effect of FBT (100 to 800 μg) on pain-related anxiety was evaluated in a multicenter, open-label study in opioid-tolerant patients with chronic pain (primarily noncancer pain) experiencing one to four BTcP episodes daily [21]. The study did not statistically significantly reduce Pain Anxiety Symptoms Scale total score (primary outcome measure) but did show significant improvements from baseline to 4 weeks in measures of cognitive anxiety, depression, and pain interference [21]. In another study in opioid-tolerant cancer patients, BPI scores significantly improved from baseline after 6 months of BTcP treatment with open-label sublingual fentanyl orally disintegrating tablet (ODT) [22]. Similarly, a phase 4 study of sublingual fentanyl ODT for BTcP in opioid-tolerant cancer patients demonstrated statistically significant improvements in daily functioning and reductions in the prevalence of anxiety and depression over a 28-day observation period [23]. Hence, the current findings are consistent with a growing body of literature indicating that effective management of BTcP can significantly improve patient QOL.

In the current study, 83 % of patients found FBT easy/very easy to use, and levels of satisfaction with FBT were significantly greater than they were at baseline with prior therapy. Patients also reported greater satisfaction with rapidity and adequacy of pain relief with FBT compared with previous BTcP medication. These findings are consistent with those reported for other rapid-onset opioids [24, 25]. The relatively low overall frequency of treatment-related AEs in the current study (6.7 % of patients reported at least one in the treatment period) [16] may have contributed to the high rates of patient satisfaction with FBT, although the open-label design of the study may have also led to underreporting of AEs.

A relatively low incidence of treatment-related AEs (16.1 %) was reported in the continuation phase of this study, during which patients received FBT for a median of 115.0 days. No new safety concerns were suggested with extended use of FBT. The most frequently observed AEs were characteristic of patients with cancer and receiving opioid therapy. The use of fentanyl-based maintenance therapy with FBT did not substantially modify the safety profile observed with use of ongoing opioid maintenance therapy.

Several limitations of the current findings should be considered. The study had an open-label design and the two arms

of the study consisted of different doses of the same formulation (rather than different formulations). Additionally, observed therapeutic effects of FBT may be related, at least in part, to other, uncontrolled factors, such as patient bias (e.g., "placebo effect"). The use of rescue medication for BTcP episodes that did not resolve with FBT treatment was permitted; concurrent use of rescue medication may have influenced observed decreases in interference in functioning and ratings of treatment satisfaction and overall status. The extent of this influence, however, is likely limited, as BTcP episodes for which rescue medication was used were relatively infrequent (8.5 % of episodes during the treatment period) [16]. The 4-week treatment period was brief and did not allow characterization of changes in QOL with longer-term FBT therapy for BTcP. Notably, previous studies characterizing BTcP were conducted at single clinical sites and evaluated relatively homogeneous patient populations [1, 2, 4, 5] and thus may not be generalizable to a broader population. By contrast, the current study was carried out at 135 sites across seven European countries and included a more demographically and clinically diverse patient population than previously described.

Conclusions

A variety of strategies are used to manage BTcP, including treatment of the underlying cause of the pain, avoidance or treatment of the precipitating factors of the pain, modification of the background analgesic regimen ("around the clock medication"), use of "rescue medication" ("breakthrough medication"), use of non-pharmacologic methods, and use of interventional techniques [7]. However, the cornerstone of the management of BTcP episodes is the use of rescue medication and, in most cases, the most appropriate rescue medication will be an opioid analgesic. The choice of opioid analgesic depends on a variety of factors [7], but there is undoubtedly a role for both the traditional oral opioid formulations and the newer rapid onset (transmucosal) opioid formulations.

The current study provides additional data to support the efficacy and short- and long-term safety of FBT; it also provides evidence that the effective management of BTcP episodes with FBT has the potential to improve patient mood and physical functioning (which are critical secondary outcomes for management).

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Conflict of interest The authors have full control of all primary data and allow the journal to review these data if requested. A. Davies has received honoraria from Cephalon and Teva Pharmaceuticals for speaking at symposia and attending advisory boards, as well as unrestricted funding to support research. H. G. Kress has received honoraria as a speaker and consultant from Cephalon/Teva Pharmaceuticals. At the time of this study, H. Schneid was an employee of Cephalon, Inc. (Maisons-Alfort, France), now a wholly owned subsidiary of Teva Pharmaceuticals (Petah Tikva, Israel).

References

1. Portenoy RK, Hagen NA (1990) Breakthrough pain: definition, prevalence and characteristics. Pain 41:273–281
2. Portenoy RK, Payne D, Jacobsen P (1999) Breakthrough pain: characteristics and impact in patients with cancer pain. Pain 81:129–134
3. Portenoy RK, Bruns D, Shoemaker B, Shoemaker SA (2010) Breakthrough pain in community-dwelling patients with cancer pain and noncancer pain, part 1: prevalence and characteristics. J Opioid Manag 6:97–108
4. Zeppetella G, O'Doherty CA, Collins S (2000) Prevalence and characteristics of breakthrough pain in cancer patients admitted to a hospice. J Pain Symptom Manag 20:87–92
5. Hwang SS, Chang VT, Kasimis B (2003) Cancer breakthrough pain characteristics and responses to treatment at a VA medical center. Pain 101:55–64
6. Caraceni A, Bertetto O, Labianca R et al (2012) Episodic (breakthrough) pain prevalence in a population of cancer pain patients. Comparison of clinical diagnoses with the QUDEI—Italian questionnaire for intense episodic pain. J Pain Symptom Manag 43: 833–841
7. Davies AN, Dickman A, Reid C, Stevens AM, Zeppetella G (2009) The management of cancer-related breakthrough pain: recommendations of a task group of the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland. Eur J Pain 13:331–338
8. Mercadante S, Radbruch L, Caraceni A et al (2002) Episodic (breakthrough) pain: consensus conference of an expert working group of the European Association for Palliative Care. Cancer 94: 832–839
9. Portenoy RK, Bruns D, Shoemaker B, Shoemaker SA (2010) Breakthrough pain in community-dwelling patients with cancer pain and noncancer pain, part 2: impact on function, mood, and quality of life. J Opioid Manag 6:109–116
10. Caraceni A, Martini C, Zecca E et al (2004) Breakthrough pain characteristics and syndromes in patients with cancer pain. An international survey. Palliat Med 18:177–183
11. FENTORA (2013) (fentanyl buccal tablet) [package insert]. Cephalon, Inc., Frazer
12. (2011) Effentora buccal tablets [package insert]. Maisons-Alfort, France: Cephalon Europe
13. Portenoy RK, Taylor D, Messina J, Tremmel L (2006) A randomized, placebo-controlled study of fentanyl buccal tablet for breakthrough pain in opioid-treated patients with cancer. Clin J Pain 22:805–811
14. Slatkin NE, Xie F, Messina J, Segal TJ (2007) Fentanyl buccal tablet for relief of breakthrough pain in opioid-tolerant patients with cancer-related chronic pain. J Support Oncol 5:327–334
15. Weinstein SM, Messina J, Xie F (2009) Fentanyl buccal tablet for the treatment of breakthrough pain in opioid-tolerant patients with

chronic cancer pain: a long-term, open-label safety study. Cancer 115:2571–2579
16. Kleeberg UR, Davies A, Jarosz J et al (2014) Pan-European, open-label dose titration study of fentanyl buccal tablet in patients with breakthrough cancer pain. Eur J Pain. doi:10.1002/ejp.577
17. International Conference on Harmonisation Working Group ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6 (R1). International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; June 10, 1996; Washington, DC. Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf. Accessed March 1, 2011
18. Portenoy RK, Miransky J, Thaler HT et al (1992) Pain in ambulatory patients with lung or colon cancer. Prevalence, characteristics, and effect. Cancer 70:1616–1624
19. Taylor DR, Webster LR, Chun SY et al (2007) Impact of breakthrough pain on quality of life in patients with chronic, noncancer pain: patient perceptions and effect of treatment with oral transmucosal fentanyl citrate (OTFC, ACTIQ). Pain Med 8:281–288
20. Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM (2001) Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 94:149–158
21. Webster LR, Messina J, Xie F, Nalamachu S (2011) Effect of fentanyl buccal tablet on pain-related anxiety: a 4-week open-label study among opioid-tolerant patients with chronic and breakthrough pain. J Opioid Manag 7:297–308
22. Nalamachu S, Hassman D, Wallace MS, Dumble S, Derrick R, Howell J (2011) Long-term effectiveness and tolerability of sublingual fentanyl orally disintegrating tablet for the treatment of breakthrough cancer pain. Curr Med Res Opin 27:519–530
23. Uberall MA, Muller-Schwefe GH (2011) Sublingual fentanyl orally disintegrating tablet in daily practice: efficacy, safety and tolerability in patients with breakthrough cancer pain. Curr Med Res Opin 27:1385–1394
24. Davies A, Sitte T, Elsner F et al (2011) Consistency of efficacy, patient acceptability, and nasal tolerability of fentanyl pectin nasal spray compared with immediate-release morphine sulfate in breakthrough cancer pain. J Pain Symptom Manag 41:358–366
25. Mercadante S, Radbruch L, Davies A et al (2009) A comparison of intranasal fentanyl spray with oral transmucosal fentanyl citrate for the treatment of breakthrough cancer pain: an open-label, randomised, crossover trial. Curr Med Res Opin 25:2805–2815