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FENTORA LONG-TERM SAFETY STUDY (The Weinstein Study)

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Objective: This long-term, open-label, multicenter study was conducted to evaluate the safety and tolerability of treatment with *FENTORA*® (fentanyl citrate) buccal tablet [C-II] to manage breakthrough pain (BTP) in opioid-tolerant patients with chronic cancer pain.

Introduction: The study described in this reprint is an open-label extension (OLE) study into which patients who had participated in short-term clinical trials were given an opportunity to continue receiving *FENTORA* during the time before it became commercially available. One of these short-term studies was the pivotal trial upon which FDA approval of *FENTORA* was based, which you also know as the Portenoy study. In addition to patients from these two short-term clinical trials, the study was open to opioid-tolerant patients with cancer who had not previously been treated with *FENTORA*.

HOW TO USE THIS SMART PDF

This Smart PDF allows you to review the Weinstein study in several ways:

Menu The Reprint Menu allows you to quickly find specific information within the body of the study

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Questions The Self-Check Questions allow you to test your knowledge of key facts about the study and its findings to ensure that you have a complete understanding of the study design, results and safety information in the pivotal trial for *FENTORA*.

When presenting the approved clinical reprint to Healthcare Professionals (HCPs), you should refer to the approved Training Guide (FEN-2247)

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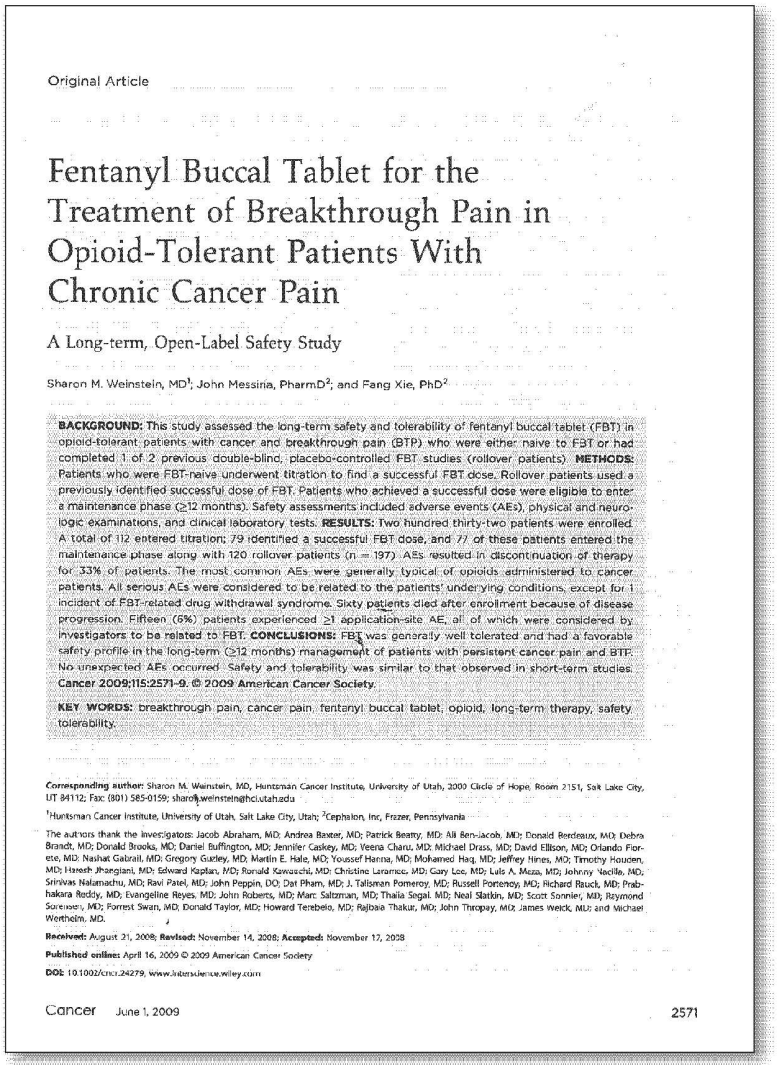

Original Article

Fentanyl Buccal Tablet for the Treatment of Breakthrough Pain in Opioid-Tolerant Patients With Chronic Cancer Pain

A Long-term, Open-Label Safety Study

Sharon M. Weinstein, MD[1]; John Messina, PharmD[2]; and Fang Xie, PhD[2]

BACKGROUND: This study assessed the long-term safety and tolerability of fentanyl buccal tablet (FBT) in opioid-tolerant patients with cancer and breakthrough pain (BTP) who were either naive to FBT or had completed 1 of 2 previous double-blind, placebo-controlled FBT studies (rollover patients). **METHODS:** Patients who were FBT-naive underwent titration to find a successful FBT dose. Rollover patients used a previously identified successful dose of FBT. Patients who achieved a successful dose were eligible to enter a maintenance phase (≥12 months). Safety assessments included adverse events (AEs), physical and neurologic examinations, and clinical laboratory tests. **RESULTS:** Two hundred thirty-two patients were enrolled. A total of 112 entered titration; 79 identified a successful FBT dose, and 77 of these patients entered the maintenance phase along with 120 rollover patients (n = 197). AEs resulted in discontinuation of therapy for 33% of patients. The most common AEs were generally typical of opioids administered to cancer patients. All serious AEs were considered to be related to the patients' underlying conditions, except for 1 incident of FBT-related drug withdrawal syndrome. Sixty patients died after enrollment because of disease progression. Fifteen (6%) patients experienced ≥1 application-site AE, all of which were considered by investigators to be related to FBT. **CONCLUSIONS:** FBT was generally well tolerated and had a favorable safety profile in the long-term (≥12 months) management of patients with persistent cancer pain and BTP. No unexpected AEs occurred. Safety and tolerability was similar to that observed in short-term studies. **Cancer 2009;115:2571–9. © 2009 American Cancer Society.**

KEY WORDS: breakthrough pain, cancer pain, fentanyl buccal tablet, opioid, long-term therapy, safety, tolerability.

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1a It is important for HCPs to realize that patients with cancer on ATC opioid medications can still experience breakthrough pain (BTP) throughout the day. The majority (65%) of patients with cancer with controlled persistent pain experience transitory moderate to severe exacerbations, or flares of pain referred to as BTP.

1b The impact of breakthrough pain on activities of daily living and mood in patients with cancer is addressed in greater detail here. Cancer patients with BTP typically experience more depression and anxiety and report a worse impact of pain on their quality of life compared with cancer patients who do not have BTP.

2 This passage provides a clear description of the inadequacy of short-acting orally administered therapies (SAOs) for managing breakthrough pain in opioid tolerant patients with cancer. While episodes of BTP often reach their peak intensity within a matter of minutes, traditional SAOs can take up to 30 to 60 minutes to begin delivering their analgesic effect.

3 One of the two short-term trials from which participants were recruited for this trial was the pivotal *FENTORA* trial, which is the subject of the Portenoy reprint.

4 This long-term safety and tolerability study was designed in part as an open-label extension of clinical trials in which opioid tolerant patients with cancer with breakthrough pain had been successfully treated with *FENTORA*. However, opioid tolerant patients with cancer with BTP who had not previously received *FENTORA* were also allowed to enroll in the trial.

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The majority (65%) of cancer patients with controlled, persistent pain experience transitory moderate to severe exacerbations, or flares, of pain referred to as breakthrough pain (BTP).[1,2] Cancer patients with BTP typically experience more depression and anxiety and report a worse impact of pain on their quality of life compared with cancer patients who do not have BTP.[3] The current treatment strategy for the management of patients with moderate to severe chronic, persistent cancer pain is often an around-the-clock (ATC) opioid regimen to control persistent pain, with a short-acting, orally administered opioid as supplemental ("rescue") medication taken as needed for the management of BTP.[4-6] Current BTP treatments are often not ideal for providing effective pain relief.[7] The reason for this may be a mismatch between the temporal characteristics of BTP and the onset of analgesia associated with typical short-acting, orally administered opioids.[8] Episodes of BTP often reach peak intensity within a few minutes,[3,8,9] whereas the onset of analgesia of traditional short-acting oral opioids can take up to 30 to 60 minutes.[7,10,11]

In contrast, fentanyl buccal tablet (FBT) (Fentora; Cephalon, Inc, Frazer, Pa) is designed to provide fast onset of analgesia by enhancing fentanyl absorption across the buccal mucosa.[12] FBT is currently indicated only for the treatment of BTP in patients with cancer who are already receiving and who are tolerant of opioid therapy for their underlying persistent cancer pain.[13] Patients considered to be tolerant are those who are receiving either at least 60 mg of oral morphine per day, at least 25 μg of transdermal fentanyl per hour, at least 30 mg of oxycodone per day, at least 8 mg of oral hydromorphone per day, or an equivalent dose of another opioid for ≥1 week.

In 2 previous short-term, double-blind, randomized, placebo-controlled studies among opioid-tolerant patients with cancer-related persistent pain and BTP, analgesic activity with FBT was detected as early as 10 minutes[14] and 15 minutes,[13] respectively, after self-administration. Patients who completed either of these 2 studies and continued to have BTP episodes that were adequately controlled with FBT were offered the option of continuing treatment in a long-term (≥12 months) study to assess the ongoing safety and tolerability of FBT. Thus, the current study served as a long-term, open-label extension for patients from the 2 previous double-blind, placebo-controlled studies. This study also enrolled new patients currently being managed with ATC opioids but naive to FBT.

The objectives of the current study were to determine the long-term tolerability and safety of FBT as well as the patient-assessed FBT medication performance, and to assess the development of incremental tolerance in opioid-tolerant cancer patients with cancer-related BTP.

MATERIALS AND METHODS

This open-label study was conducted at 47 centers in the US between April 2004 and November 2006. The study was originally designed for 12 months of maintenance. An extension was added so that patients could continue in the study through November 30, 2006, at which point the study was terminated once FBT became commercially available.

The study was conducted in accordance with good clinical practice,[15] and the protocol was approved by the institutional review board at each center. All patients provided written informed consent.

Patients

Opioid tolerant men and women (aged ≥18 years) who had pain associated with a histologically documented malignant solid tumor or hematologic malignancy and had a life expectancy of ≥2 months were eligible to enroll. Patients who were naive to FBT and patients who had completed 1 of 2 previous randomized, controlled FBT studies[13,14] (rollover patients) were eligible. Inclusion criteria included the use of a fixed-dose ATC opioid regimen (ie, morphine at a dose of 60-1000 mg/day, transdermal fentanyl at a dose of 25-300 μg/hour, or the morphine equivalent) for persistent cancer-related pain for ≥1 week and the occurrence of an average of 1 to 4 episodes of BTP per day that were treated with a previously identified dose of FBT (rollover patients) or other supplemental opioids (FBT-naive patients).

Exclusion criteria included sleep apnea or active brain metastases with increased intracranial pressure, chronic obstructive pulmonary disease, renal or hepatic function test results outside prespecified limits, a recent history of substance abuse or neurologic or psychiatric impairment that might compromise data collection, receipt of therapy ≤30 days before entering the study that

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5a The objectives of this study were to assess the long-term safety and tolerability of *FENTORA*, to gather information about patients' perceptions of the product, and to determine whether incremental tolerance to the beneficial effects of *FENTORA* would develop as a result of longer-term use.

5b The long-term safety study was open-label, which means that all participants knew that they were receiving *FENTORA*. Although originally designed to run for 12 months of maintenance therapy, an extension phase was added so that patients benefiting from *FENTORA* could continue to receive it prior to commercialization.

6 As in the pivotal trial, all of the patients in the long-term safety study were opioid-tolerant men and women aged 18 years and older who had pain associated with a histologically documented malignant solid tumor or hematologic malignancy and had a life expectancy of at least 2 months. Patients were taking commoly prescribed ATC opioid agents such as morphine, transdermal fentanyl, or the morphine equivalent.

7 Figure 1 schematically depicts the various phases of the long-term safety study. Patients who had not previously received *FENTORA* or who had discontinued treatment and therefore required re-titration of their *FENTORA* dose were required to go through a screening process and titration phase before entering the maintenance phase of the study, while those who had been receiving *FENTORA* as part of a short-term clinical trial were able to proceed directly to the maintenance phase. The maintenance phase of the study continued for one year; after this, patients who continued to benefit from *FENTORA* were given the option of enrolling in a maintenance extension phase. Patients were allowed to continue in the maintenance extension phase until *FENTORA* was approved for clinical use, at which time the long-term safety study was terminated.

8 In this study, a successful dose of *FENTORA* was defined as the first dose during the titration phase that adequately relieved the patient's breakthrough pain within 30 minutes and without unacceptable adverse effects for two successive episodes of BTP occurring at least 4 hours apart. In clinical practice, patients should be titrated to the lowest dose of *FENTORA* that provides adequate analgesia with tolerable side effects.

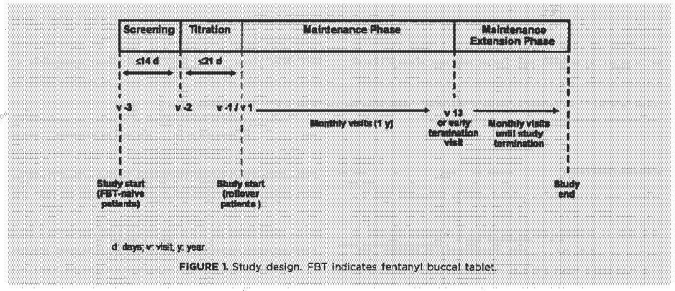

FIGURE 1. Study design. FBT indicates fentanyl buccal tablet.

would alter pain or responses to analgesics (eg, nerve blocks, anesthetic procedures), a primary source of BTP not related to cancer or cancer treatment, and the use of concomitant medications that might increase the risk of opioid-related adverse events (AEs). Women were excluded if they were pregnant or lactating, or were unwilling to practice a reliable form of contraception during the study.

Study Design

The study consisted of screening, titration, and maintenance phases (Fig. 1). New patients participated in a titration phase (≤21 days). All patients (both newly titrated and rollover) entered the maintenance treatment phase of ≥12 months. At the screening visit, FBT-naive patients underwent physical, laboratory, and neurologic examinations, including an examination of the oral mucosa and measurements of vital signs. Rollover patients underwent these procedures at the first maintenance visit. All patients continued to take their ATC opioid regimens for persistent pain throughout the titration and maintenance phases. Adjustments to the ATC dosing regimen were allowed.

The successful dose of FBT was defined as the dose during titration that adequately relieved BTP within 30 minutes without unacceptable AEs for 2 successive episodes of BTP (occurring ≥4 hours apart). The titration procedure for FBT has been published elsewhere.[13,14] Briefly, all patients received a single tablet of FBT as a test dose. If the FBT dose was tolerated, then the patient entered the titration phase. Patients who had not been receiving the earlier formulation of oral transmucosal fentanyl citrate (OTFC) before study entry received a test dose of FBT of 100 μg. Patients who had been receiving OTFC to manage BTP received a protocol-defined FBT dose based on their prestudy OTFC dose: those who were previously being treated with OTFC at a dose of ≤600 μg were administered a test dose of FBT of 100 μg, and those previously receiving either 800 μg, 1200 μg, or 1600 μg of OTFC were given a test dose of FBT of 200 μg, 400 μg, or 600 μg, respectively. During titration, patients self-administered FBT to treat a BTP episode. A single tablet was placed between the upper gum and cheek, above a molar tooth, and allowed to dissolve. After taking FBT for a BTP episode, patients were required to wait ≥4 hours before taking FBT again. However, if pain relief was not adequate by 30 minutes, patients could take their standard supplemental medications. By taking increasingly higher doses of FBT as necessary for successive episodes of BTP, patients identified a successful FBT dose (100 μg, 200 μg, 400 μg, 600 μg, or 800 μg) for the treatment of BTP during the maintenance phase. Patients who did not obtain satisfactory relief of BTP at the highest FBT dose (800 μg) were discontinued from the study.

Patients who identified a successful FBT dose during titration were eligible to enter maintenance treatment. During maintenance, if a patient did not obtain adequate pain relief within 30 minutes after self-administration of FBT, he or she could take a second tablet. If a patient required more than a single tablet of FBT for 2 of 3 BTP

9 The titration procedure in this trial is similar but not identical to the initial dosing recommendations for *FENTORA*. Be sure that you are able to clearly understand the proper dosing of *FENTORA*, both for patients who are and are not switching from OTFC/Actiq. The required initial dose of *FENTORA* for opioid tolerant patients who are not being converted from OTFC/Actiq is always 100 mcg.

10 The range of *FENTORA* doses allowed during the maintenance phase of this trial was 100 mcg to 800 mcg. Patients who did not obtain adequate relief of BTP with an 800 mcg dose of *FENTORA* were required to discontinue the trial.

11 In this study, *FENTORA* could be used for a maximum of 6 episodes of BTP per day, with the total number of tablets not to exceed 8 per day.

12 This paragraph describes the care that was taken to ensure safe use of *FENTORA* during the long-term maintenance phase of treatment.

13 In the long-term safety study, several different approaches were used to assess the adequacy of breakthrough pain management in patients receiving *FENTORA*. Patients kept diaries recording their BTP episodes and medication use, which were reviewed by clinicians to assess the need for adjustments to the dosage of either *FENTORA* or the patient's ATC medication. In addition, patients used a 5-point scale (poor, fair, good, very good, and excellent) to rate the effectiveness of *FENTORA* in relieving their breakthrough pain on a daily basis. Finally, patients were asked to complete a questionnaire at the end of the trial comparing *FENTORA* to the medication they had previously used for control of BTP, because it was added to the protocol after the study was already under way, however, only about 25% of the study population actually filled out this questionnaire.

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episodes per day, the investigators had the option of increasing the dose. If the patient was already receiving the highest dose (800 μg), he or she was discontinued from the study. The study drug could be used for a maximum of 6 BTP episodes on any given day and a maximum of 8 tablets could be used on any given day.

Assessments

Before the maintenance phases, safety for new patients was monitored by physical and neurologic examinations and clinical laboratory tests performed at screening and at the end of titration, as well as by assessments of vital signs and examinations of the oral mucosa at screening and at the initiation and end of titration. All AEs either observed by the investigators or reported by the patients were reviewed at the end of titration. Rollover patients underwent physical and neurologic examinations, vital sign measurements, and clinical laboratory tests at the end of their previous study, and these findings served as data for Visit 1 (initiation of maintenance) of the current study.

During maintenance treatment, vital signs were measured and AEs reviewed monthly. Clinical laboratory tests and examination of the oral mucosa were performed at least every 3 months. Neurologic and physical examinations were performed at least every 3 months during the first 12 months of the study and at least every 6 months thereafter. All assessments were repeated at each patient's final visit.

Patients recorded in a diary the number of BTP episodes they had each day and the number of tablets of FBT taken per day. Patients rated the effectiveness of FBT in alleviating BTP by completing a Global Medication Performance assessment on a daily basis, using a 5-point scale (0 indicates poor, 1 indicates fair, 2 indicates good, 3 indicates very good, and 4 indicates excellent). Patients also completed a 7-item study medication questionnaire, the Patient Assessment of Medication, before and 1 month after the start of the maintenance phase. This questionnaire was an exploratory measure, added to the protocol after the study had started; thus, only 25% of patients completed the questionnaire. The questionnaire asked patients to compare FBT with their previous supplemental medications, through the following questions: 1) which medication would you prefer to use when treating your BTP? 2) which medication had a faster onset of relief? 3) which medication was easier to administer? and 4) which medication was more convenient to use? The questionnaire also asked patients to rate FBT as excellent, good, fair, or poor in relation to onset of action, ease of administration, and convenience of use.

Investigators reviewed patient diaries at each study visit to assess the need for dose adjustments for either FBT or ATC opioids. Dose increases and decreases were made at the discretion of the investigator. Specifically, investigators considered the number of BTP episodes per day, the need for more than a single tablet of FBT for BTP episodes, and Global Medication Performance scores, as well as the patient's reports of AEs and medication use, including the use of additional supplemental medication for BTP. Investigators selected the reason for any dose adjustments every month from a list of options: because of the development of incremental tolerance, to rebalance concomitant medication, because of disease progression or regression, because of a successful alternative therapy, because of the development of a safety concern or intolerability, or other reason.

Statistical Analysis

The sample size for this study was based on clinical rather than statistical considerations. It was planned that up to 100 patients who successfully completed 1 of 2 previous short-term studies would continue in this study. Patients who received a test dose of FBT for titration constituted the titration safety population. Patients who received ≥1 dose of FBT during maintenance (which included the extension) composed the maintenance safety population. Patients who received ≥1 dose of FBT during any phase of the study constituted the overall safety population. This was an open-label study; observed data were summarized using descriptive statistics, and missing data were not imputed.

RESULTS

Patient Disposition

All 232 patients enrolled in the study constituted the overall safety population because they received ≥1 dose of FBT. A total of 110 patients were FBT-naive and therefore entered titration. In addition, 2 rollover patients

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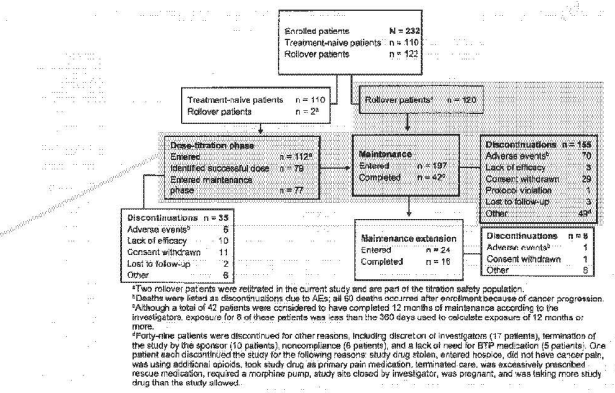
14 Figure 2 illustrates in graphic form the origin and eventual outcome for the 197 patients who made up the maintenance safety population for this study. In this diagram, "rollover patients" are participants from the pivotal trial and another short-term clinical study who elected to continue receiving *FENTORA* via the long-term safety study. Note, too, that the group of 70 patients designated as having discontinued the study as the result of an AE includes 60 individuals who died after enrollment as a result of cancer progression.

15 The 197 patients in the safety analysis population included 120 who had begun receiving *FENTORA* as part of a short-term clinical trial, 75 who had never received *FENTORA*, and 2 who had previously received *FENTORA* but required re-titration as a result of having discontinued treatment.



[a]Two rollover patients were retitrated in the current study and are part of the titration safety population.
[b]Deaths were listed as discontinuations due to AEs; all 60 deaths occurred after enrollment because of cancer progression.
[c]Although a total of 42 patients were considered to have completed 12 months of maintenance according to the investigators, exposure for 8 of these patients was less than the 360 days used to calculate exposure of 12 months or more.
[d]Forty-nine patients were discontinued for other reasons, including discretion of investigators (17 patients), termination of the study by the sponsor (10 patients), noncompliance (6 patients), and a lack of need for BTP medication (5 patients). One patient each discontinued the study for the following reasons: study drug stolen, entered hospice, did not have cancer pain, was using additional opioids, took study drug as primary pain medication, terminated care, was excessively prescribed rescue medication, required a morphine pump, study site closed by investigator, was pregnant, and was taking more study drug than the study allowed.

FIGURE 2. Patient disposition. AEs indicates adverse events; BTP, breakthrough pain.

entered titration for repeat titration of their FBT dose because their previous dose was not effective (Fig. 2). These 112 patients received the test dose of FBT and constituted the titration safety population. Of these 112 patients, 79 (71%) identified a successful dose, and 77 (69%) entered the maintenance phase; 35 (31%) discontinued during titration, including 2 patients who found a successful dose but discontinued the study. The primary reasons for discontinuation during titration included withdrawal of consent (11 patients) and lack of efficacy (10 patients).

The 120 rollover patients (not including the 2 rollover patients who retitrated their FBT dose) along with 77 newly titrated patients entered maintenance and received ≥1 dose of FBT. This population of 197 patients (85% of 232 patients) constituted the maintenance safety analysis population (Fig. 2). Forty-two patients (18% of 232 patients) remained in maintenance treatment for approximately 12 months, and 155 (67%) patients discontinued the study during that period (Fig. 2), most frequently because of AEs (n = 70 patients), the majority of which were unrelated to study drug. Only 3 (1%) patients were discontinued because of lack of efficacy (Fig. 2).

Patient Demographics and Pain Characteristics

Baseline demographics for the overall safety population, presented in Table 1, were found to be similar in the titration safety and maintenance safety populations. The pathophysiology of BTP for the overall safety population was considered to be primarily nociceptive in 107 (46%) patients, primarily neuropathic in 42 (18%) patients, and mixed (approximately 50% neuropathic/50% nociceptive) in 83 (36%) patients. Commonly used ATC and supplemental medications of patients before entry into the study are presented in Table 2. All 232 patients were receiving concomitant analgesic agents because opioid tolerance was required for study entry. A total of 223 patients (96%) were receiving medications other than analgesics; 111 (48%) were receiving antineoplastic and/or immunomodulating agents.

16 The pathophysiology of BTP for the overall safety population was considered to be primarily nociceptive in 107 (46%) patients, primarily neuropathic in 42 (18%) patients, and mixed (approximately 50% neuropathic/50% nociceptive) in 83 (36%) patients.

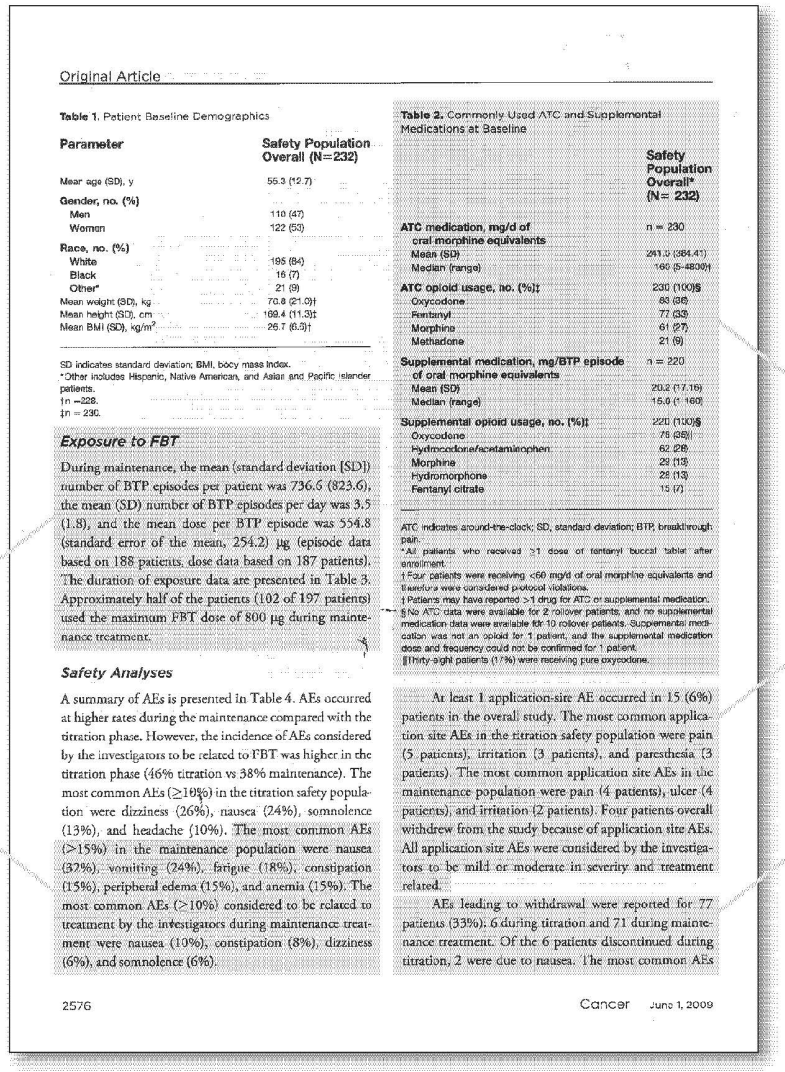


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Table 1. Patient Baseline Demographics

Parameter	Safety Population Overall (N=232)
Mean age (SD), y	55.3 (12.7)
Gender, no. (%)	
Men	110 (47)
Women	122 (53)
Race, no. (%)	
White	195 (84)
Black	16 (7)
Other*	21 (9)
Mean weight (SD), kg	70.8 (21.0)†
Mean height (SD), cm	168.4 (11.0)‡
Mean BMI (SD), kg/m^2	25.7 (6.5)†

SD indicates standard deviation; BMI, body mass index.
*Other includes Hispanic, Native American, and Asian and Pacific Islander patients.
†n = 228.
‡n = 230.

Table 2. Commonly Used ATC and Supplemental Medications at Baseline

	Safety Population Overall* (N= 232)
ATC medication, mg/d of oral morphine equivalents	n = 230
Mean (SD)	261.0 (364.41)
Median (range)	160 (5-4800)†
ATC opioid usage, no. (%)‡	230 (100)§
Oxycodone	83 (36)
Fentanyl	77 (33)
Morphine	61 (27)
Methadone	21 (9)
Supplemental medication, mg/BTP episode of oral morphine equivalents	n = 220
Mean (SD)	20.2 (17.16)
Median (range)	15.0 (1-160)
Supplemental opioid usage, no. (%)‡	220 (100)§
Oxycodone	76 (35)‖
Hydrocodone/acetaminophen	62 (28)
Morphine	29 (13)
Hydromorphone	28 (13)
Fentanyl citrate	15 (7)

ATC indicates around-the-clock; SD, standard deviation; BTP, breakthrough pain.
*All patients who received ≥1 dose of fentanyl buccal tablet after enrollment.
†Four patients were receiving <60 mg/d of oral morphine equivalents and therefore were considered protocol violations.
‡Patients may have reported >1 drug for ATC or supplemental medication.
§No ATC data were available for 2 rollover patients, and no supplemental medication data were available for 10 rollover patients. Supplemental medication was not an opioid for 1 patient, and the supplemental medication dose and frequency could not be confirmed for 1 patient.
‖Thirty-eight patients (17%) were receiving pure oxycodone.

Exposure to FBT

During maintenance, the mean (standard deviation [SD]) number of BTP episodes per patient was 736.6 (823.6), the mean (SD) number of BTP episodes per day was 3.5 (1.8), and the mean dose per BTP episode was 554.8 (standard error of the mean, 254.2) µg (episode data based on 188 patients, dose data based on 187 patients). The duration of exposure data are presented in Table 3. Approximately half of the patients (102 of 197 patients) used the maximum FBT dose of 800 µg during maintenance treatment.

Safety Analyses

A summary of AEs is presented in Table 4. AEs occurred at higher rates during the maintenance compared with the titration phase. However, the incidence of AEs considered by the investigators to be related to FBT was higher in the titration phase (46% titration vs 38% maintenance). The most common AEs (≥10%) in the titration safety population were dizziness (26%), nausea (24%), somnolence (13%), and headache (10%). The most common AEs (>15%) in the maintenance population were nausea (32%), vomiting (24%), fatigue (18%), constipation (15%), peripheral edema (15%), and anemia (15%). The most common AEs (≥10%) considered to be related to treatment by the investigators during maintenance treatment were nausea (10%), constipation (8%), dizziness (6%), and somnolence (6%).

At least 1 application-site AE occurred in 15 (6%) patients in the overall study. The most common application site AEs in the titration safety population were pain (5 patients), irritation (3 patients), and paresthesia (3 patients). The most common application site AEs in the maintenance population were pain (4 patients), ulcer (4 patients), and irritation (2 patients). Four patients overall withdrew from the study because of application site AEs. All application site AEs were considered by the investigators to be mild or moderate in severity and treatment related.

AEs leading to withdrawal were reported for 77 patients (33%): 6 during titration and 71 during maintenance treatment. Of the 6 patients discontinued during titration, 2 were due to nausea. The most common AEs

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17 Patients in this study experienced an average of 3.5 episodes of breakthrough pain per day, and required an average *FENTORA* dose of 555 mcg per episode to manage their BTP. Roughly half of the study population (102 of 197 patients) required the maximum allowable dose of *FENTORA*, which was 800 mcg per episode.

18 AEs occurring in at least 15% of patients in the maintenance population were nausea (32%), vomiting (24%), fatigue (18%), constipation (15%), peripheral edema (15%), and anemia (15%). The most common AEs that were considered by investigators to be related to treatment during the maintenance phase were nausea (10%), constipation (8%), dizziness (6%), and somnolence (6%).

19 All of the patients in the long-term safety trial were opioid tolerant. Table 2 lists the ATC medications these patients were receiving for their underlying persistent cancer pain, which included oxycodone (36%), fentanyl (33%), morphine (27%), and methadone (9%).

20 Adverse application site reactions were reported by 15 patients, representing 6% of the overall study population. During the maintenance phase of the trial, the most common application site reactions were pain, irritation, paresthesia (tingling), and ulceration. All adverse reactions involving the application site were considered to be mild to moderate in severity; however, 4 patients withdrew from the study because of application site reactions.

21 AEs leading to withdrawal from the long-term safety study were reported for 77 patients, representing 33% of the study population. The majority of discontinuations during the maintenance phase of the trial were related to the patients' underlying disease; for example, 53 patients discontinued treatment because of cancer progression.

Table 3. Exposure to FBT

Parameter	Safety Population Titration (n = 112)	Maintenance (n = 197)
Duration of exposure, d		
Mean (SD)	6.5 (6.5)	181.5 (166.3)
Median (range)	5 (1-46)	122 (1-666)
Patients exposed to FBT,* no. (%)		
≥3 mo		121 (61)
≥6 mo		74 (38)
≥12 mo		36 (18)†

FBT indicates fentanyl buccal tablet; SD, standard deviation.
* Months were determined based on exposure in days, in which ≥360 days of exposure was required to be considered as having an exposure of ≥12 months.
† A total of 42 patients were considered to have completed this study. However, exposure for 8 of these patients was <360 days, which was used to calculate exposure of ≥12 months, and they are not counted in this table. In addition, 2 of the patients who completed 12 months of treatment were not considered to have completed the maintenance phase (1 patient died and 1 patient discontinued treatment).

leading to discontinuation during maintenance treatment were related to the patients' underlying disease; neoplasms (benign, malignant, and unspecified) accounted for the withdrawal of 53 patients.

All serious AEs were considered to be related to patients' underlying conditions except for 1 serious AE of drug withdrawal syndrome, which was deemed by the investigator to be related to study drug treatment. No cases of respiratory depression were considered by the investigators to be related to study drug administration. No incidences of overdose were reported.

Sixty patients died after enrollment in the study; all deaths were attributable to progression of cancer or pathology of underlying disease. Of these 60 patients, 2 died as a result of AEs that developed during the titration phase (1 due to disease progression and 1 due to cerebral hemorrhage), and 58 died of AEs that developed during or after the maintenance phase. Included in the 60 deaths were 4 that were attributable in part to serious AEs that developed >30 days after the discontinuation of FBT.

Three patients had a history of mucositis before entering the study, and 5 patients developed mucositis during the study (4 mild cases and 1 moderate case). The investigators considered these developments to be unrelated to FBT administration. Two of these patients subsequently withdrew from the study, for reasons unrelated to mucositis.

Table 4. Summary of Adverse Events*

	Safety Population Overall (N = 232) (%)	Titration (n = 112) (%)	Maintenance (n = 197) (%)
Patients with ≥1 AE	208 (90)	68 (61)	184 (93)
AEs occurring in ≥5% of patients*			
Nausea	86 (37)	27 (24)	63 (32)
Vomiting	52 (22)	4 (4)	48 (24)
Dizziness	46 (20)	29 (26)	21 (11)
Fatigue	38 (16)	3 (3)	35 (18)
Constipation	33 (14)	3 (3)	30 (15)
Anemia	32 (14)	3 (3)	29 (15)
Headache	32 (14)	11 (10)	24 (12)
Somnolence	30 (13)	14 (13)	18 (9)
Peripheral edema	29 (13)	0	29 (15)
Abdominal pain	25 (11)	2 (2)	23 (12)
Dehydration	25 (11)	2 (2)	23 (12)
Anorexia	23 (10)	0	23 (12)
Depression	23 (10)	0	22 (12)
Diarrhea	23 (10)	3 (3)	20 (10)
Pneumonia	21 (9)	1 (<1)	20 (10)
Asthenia	19 (8)	0	19 (10)
Pyrexia	19 (8)	1 (<1)	18 (9)
Weight decrease	19 (8)	2 (2)	17 (9)
Dyspnea	18 (8)	0	18 (9)
Anxiety	16 (7)	1 (<1)	15 (8)
Back pain	16 (7)	1 (<1)	15 (8)
Arthralgia	15 (6)	0	15 (8)
Confusional state	15 (6)	1 (<1)	14 (7)
Cough	14 (6)	2 (2)	13 (7)
Insomnia	14 (6)	1 (<1)	13 (7)
Hypokalemia	13 (6)	0	13 (7)
Urinary tract infection	13 (6)	2 (2)	11 (6)
Cancer pain	12 (5)	0	12 (6)
Neutropenia	12 (5)	0	12 (6)
Pruritus	12 (5)	3 (3)	10 (5)
Stomatitis	12 (5)	2 (2)	10 (5)
Dyspepsia	11 (5)	0	11 (6)
Hypotension	10 (4)	0	10 (5)
Hypoesthesia	9 (4)	1 (<1)	9 (5)
Pharyngolaryngeal pain	9 (4)	0	9 (5)

AE indicates adverse event.
* Patients may have reported >1 AE.

No clinically meaningful trends were observed in laboratory values, including serum chemistry and hematology. Most abnormal hematology findings were consistent with the patient's medical history, abnormal findings at baseline, or anticancer therapy. Changes in physical and neurologic examinations were also considered to be consistent with the medical conditions observed in patients with cancer.

Secondary Measures

Patients compared FBT with their previous supplemental medication using a 7-item Patient Assessment of

22 The only serious AE in this trial that was considered to be related to *FENTORA* was drug withdrawal, which occurred in one patient. No cases of respiratory depression occurred that were considered by the investigators to be related to *FENTORA*.

23 All deaths that occurred during the long-term safety study (60 patients) were attributed either to cancer progression or to the underlying disease pathology.

24 Table 4 lists the incidence of AEs reported by at least 5% of patients during the trial as a whole, during the titration phase, or during the maintenance phase. Notice that AEs generally occurred at a higher rate during the maintenance phase than during the titration phase of the trial. However, specific AEs that were considered to be related to *FENTORA*, such as dizziness and somnolence, had a higher incidence during the titration phase than during the maintenance phase.

Table 5. Dose Adjustments From Original Successful Dose to Final Dose at the Last Study Visit (Maintenance Safety Population)

Final Dose, No. (%)	Successful Dose, No. (%)*				
	100 µg (n = 15)	200 µg (n = 26)	400 µg (n = 43)	600 µg (n = 51)	800 µg (n = 62)
100 µg (n = 11)	11 (73)	0	0	0	0
200 µg (n = 20)	2 (13)	15 (58)	2 (5)	1 (2)	0
400 µg (n = 35)	1 (7)	8 (31)	23 (53)	3 (6)	0
600 µg (n = 39)	1 (7)	2 (8)	8 (21)	26 (51)	1 (2)
800 µg (n = 92)	0	1 (4)	9 (21)	21 (41)	61 (98)

* Successful fentanyl buccal tablet doses were identified either during the titration phase (in treatment-naive patients) or during the previous studies (rollover patients). Shaded areas indicate that the final dose was the same as the initial dose in a total of 136 patients (69%) (including any patients who had dose changes during the study and were changed back to their initial dose).

Medication after 1 month of maintenance. Patients favored FBT compared with their previous BTP medication in terms of overall preference (88% FBT vs 12% previous BTP medication; n = 81), time to onset of pain relief (95% vs 5%; n = 81), ease of administration (66% vs 34%; n = 82), and convenience of use (68% vs 32%; n = 82). The majority of patients rated FBT as either excellent or good for onset of action (93%; n = 82), convenience of use (82%; n = 82), and ease of administration (80%; n = 82).

On the Global Medication Performance questionnaire, on average patients rated FBT between good and very good throughout maintenance. The mean (SD) Global Medication Performance was 2.4 (0.9) at the initiation of maintenance (n = 187) and 2.3 (0.8) at endpoint (n = 188). Scores were relatively stable for patients who stayed in the study until its end (Global Medication Performance rating at 18 months was 2.1 [0.6]; n = 10).

The majority of patients did not have dose changes over time; the final dose of FBT at the last study visit was the same as the initial successful dose for 136 of 197 (69%) patients (including 3 patients who had dose changes during the study and eventually changed back to the initial dose) (Table 5). Compared with the initial dose, the final dose was higher for 54 patients and lower for 7 patients.

DISCUSSION

FBT was generally well tolerated and had a favorable safety profile during the long-term treatment of BTP in opioid-tolerant patients with chronic persistent cancer pain. The most frequently reported AEs were of the type and severity expected in patients being treated with ATC opioids (ie, nausea, dizziness, vomiting, somnolence, and constipation).[6,16] Overall, the incidence of AEs was higher than in short-term studies of FBT in patients with cancer and BTP,[13,14] as would be expected based on the extended duration of the current study.

A successful FBT dose was identified by 71% of patients during titration, a percentage similar to the rates observed in previous studies of FBT in patients with cancer and BTP.[13,14] Treatment with FBT demonstrated control of BTP for ≥12 months. The majority of patients had a final dose that was the same as their initial successful dose, suggesting there was no decline in analgesic efficacy over time in most patients. This is supported by the observation that only 3 (1%) patients discontinued the study because of the lack of efficacy of FBT during the maintenance phase.

The current study was not intended as a rigorous examination of the development of tolerance to the analgesic effects of FBT over time. An increase from an initially successful dose of FBT may indicate cancer progression and an increase in the severity of cancer pain and cancer-related BTP that may ensue. Indeed, it is generally accepted that increasing pain due to disease progression is the primary reason for dose escalation in patients with cancer and BTP.[15] An increase in FBT dose could also reflect a discrepancy between the patient's expectation of pain relief and the degree of relief actually achieved, and/or an increase in the amount or level of patient daily activity because of effective BTP management. Clinical

25 In their discussion of long-term safety study results, the authors point out that the majority of patients ended the trial receiving the same dose of *FENTORA* they began receiving during the titration phase, and only three patients discontinued treatment during the maintenance phase as a result of efficacy issues.

experience has shown that patients with functional goals may increase their activity until the maximum tolerable pain level is reached.

The Global Medication Performance scores, which were consistent with those in previous studies,[13,14] indicated that patients who remained in the study continued to be satisfied over time with the effectiveness of FBT. Patients clearly preferred FBT to previous BTP medications, as indicated by Patient Assessment of Medication scores, which were also consistent with those noted in previous short-term studies of FBT in a similar patient population.[13,14]

The potential limitations of this study are its open-label study design with no active comparator and the large attrition rate, which limited the ability to draw conclusions. However, the rate of attrition is typically unavoidable in a population with progressive disease, such as the one in this study.

Conclusions

To our knowledge, the current study is the first to follow a large patient population with chronic cancer pain for ≥12 months in the evaluation of FBT for the management of BTP. FBT was generally well tolerated and had a favorable safety profile. Unexpected AEs did not occur, thus confirming and extending the findings of previous short-term studies. Response to FBT was maintained over the period ≥12 months.

Conflict of Interest Disclosures

This study was sponsored by Cephalon, Inc. Writing assistance was provided by Embryon. Drs. Messina and Xie are both employees of Cephalon, Inc.

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SELF-CHECK QUESTIONS

1. Participants in the long-term safety study included:

   A. Patients who had completed a short-term clinical trial of *FENTORA*

   B. Patients who had previously taken but discontinued *FENTORA*

   C. Patients who had never taken *FENTORA*

   D. All of the above

   E. None of the above

2. Briefly explain how an effective dose of *FENTORA* was determined for each participant in the long-term safety study.

   _____

   _____

   _____

3. The maintenance phase of the long-term safety study included _____ patients, _____ of whom used the maximum *FENTORA* dose of _____ mcg during maintenance treatment.

4. List the 4 most common AEs considered to be related to treatment during the maintenance phase of the long-term safety study.

   _____

   _____

   _____

   _____

ANSWERS

1. D
2. Participants received increasingly higher doses of *FENTORA* until a dose was identified that adequately relieved BTP within 30 minutes and without unacceptable adverse effects for 2 successive episodes of BTP occuring at least 4 hours apart.
3. 197; about half (102 of 197); 800
4. Nausea, constipation, dizziness, somnolence

CNS