Support Care Cancer (2016) 24:2669–2675
DOI 10.1007/s00520-015-3056-3

ORIGINAL ARTICLE

Long-term safety of fentanyl sublingual spray in opioid-tolerant patients with breakthrough cancer pain

Harold Minkowitz[1] · **Janet Bull**[2] · **R. Charles Brownlow**[3] · **Neha Parikh**[4] · **Richard Rauck**[5]

Received: 27 October 2015 / Accepted: 7 December 2015 / Published online: 16 January 2016

Abstract
Purpose The current study assessed the long-term safety of fentanyl sublingual spray for managing breakthrough cancer pain (BTCP).
Methods This open-label, multicenter study enrolled both de novo and rollover patients who completed a double-blind, efficacy trial. Eligible patients were ≥18 years of age and experiencing pain that was being managed with an around-the-clock opioid yet were experiencing ≤4 BTCP episodes daily and were opioid-tolerant (i.e., receiving ≥60 mg/day oral morphine or an equivalent dose of another opioid for ≥1 week). De novo patients initially entered a 21-day titration period to identify an effective dose of fentanyl sublingual spray (100–1600 μg), then entered a 90-day maintenance period. The incidence of adverse events (AEs), results of laboratory tests, vital sign assessments, and treatment satisfaction were assessed.
Results Of the 269 patients (de novo, 179; rollover, 90) who entered the maintenance period, 163 (60.6 %) completed the study; the primary reason for discontinuation was an AE (22.3 %). Eighty percent of patients identified an effective dose of fentanyl sublingual spray (median dose, 600 μg). The most common AEs differed from the titration period (nausea (13 %), vomiting (12 %), and somnolence (10 %)) to the maintenance period (malignant neoplasm progression (24 %), vomiting (16 %), and peripheral edema (12 %)). Few changes in laboratory parameters and vital sign assessments were observed. Patients generally reported being more satisfied with fentanyl sublingual spray than with their previous BTCP treatment.
Conclusions This long-term maintenance study demonstrated that fentanyl sublingual spray was generally safe and well tolerated for managing BTCP over a 90-day period.

Keywords Cancer pain · Breakthrough pain · Fentanyl sublingual spray · Opioids

Introduction

Breakthrough cancer pain (BTCP) describes transient episodes of pain that range from severe to excruciating in intensity and occur on top of persistent background pain that can be well controlled with around-the-clock opioid therapy [1]. Episodes of BTCP are characterized by a rapid onset and peak intensity occurring within a few minutes [1]. BTCP episodes have been reported to occur in 33 to 89 % of patients with cancer, depending on the clinical setting where the estimations were made [1–5]. The most common precipitating factors for BTCP include the end of the dosing interval for around-the-clock analgesics, as well as many common daily activities such as moving, sitting, eating, and going to the

Previous presentation: Preliminary data were presented at the 31st Annual Scientific Meeting of the American Pain Society, May, 2012, Honolulu, HI.

✉ Harold Minkowitz
Harold@Minkowitzmd.com

[1] Department of Anesthesiology, Memorial Herman Memorial City Medical Center, 921 Gessner Road, Houston, TX 77024, USA

[2] Four Seasons Hospice and Palliative Care, Flat Rock, NC, USA

[3] Better Health Clinical Research, Newnan, GA, USA

[4] Clinical Operations, INSYS Therapeutics, Inc., Chandler, AZ, USA

[5] Medical Department, Carolinas Pain Institute and The Center for Clinical Research, Winston Salem, NC, USA

bathroom [1, 3]. BTCP episodes must be managed effectively to alleviate the substantial impairments in physical functioning, psychological well-being, and quality of life of the affected patient [6].

Fentanyl is a potent, synthetic μ-opioid receptor agonist with demonstrated efficacy for treating cancer pain [7]. Several oral transmucosal immediate-release fentanyl formulations (TIRFs; e.g., lozenges, oral disintegrating tablets), which produce a rapid onset of analgesia, have been developed for the management of BTCP [7, 8]. In addition, a fentanyl sublingual spray has been shown to be efficacious and safe for treating BTCP in a double-blind, placebo-controlled pivotal efficacy trial [9] and has been approved by the US Food and Drug Administration for the management of BTCP in opioid-tolerant adults [10]. Differences in the cellular and physiologic properties of the sublingual mucosa versus other oral mucosal sites (transmucosal, buccal) facilitate the sublingual administration of fentanyl, which increases the rate and extent of absorption and could potentially improve the onset of analgesia [11]. Because many patients require BTCP management over an extended period of time, the long-term safety and tolerability of TIRFs must be determined [3]. The current study was conducted to evaluate the long-term safety and tolerability of fentanyl sublingual spray for managing BTCP.

Methods

Study design

This phase III, open-label, multicenter study (ClinicalTrials.gov; NCT00538863) was conducted in the USA, Canada, and India, approved by the appropriate ethics committees, and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All persons provided informed consent prior to their inclusion in the study. The study enrolled both de novo patients and those who had successfully completed the final visit of a pivotal double-blind clinical trial to demonstrate the efficacy of sublingual fentanyl (i.e., rollover patients [9]; Fig. 1). The eligibility for enrollment of de novo patients was determined during a 28 ± 7-day screening period. Eligible patients then entered an open-label, 21 + 5-day titration period to identify a dose of fentanyl sublingual spray that successfully managed BTCP episodes without causing intolerable adverse events (AEs). A successful fentanyl sublingual spray dose (100, 200, 400, 600, 800, 1200, or 1600 μg) was defined as one that effectively treated ≥2 consecutive BTCP episodes without intolerable AEs. Effective doses were already identified for rollover patients during the previous double-blind study. The open-label maintenance treatment period was 90 days in duration for both de novo and rollover patients. During the maintenance period, patients were allowed to treat ≤4 BTCP episodes daily, which were required to be separated by ≥4 h.

Inclusion and exclusion criteria

Inclusion and exclusion criteria were the same for de novo and rollover patients. Eligible participants were required to be ≥18 years of age and have a diagnosis of cancer; patients also had persistent pain (no more than moderate in severity) that was well controlled with stable doses of an opioid analgesic yet were experiencing an average of one to four episodes of BTCP per day. All patients were additionally required to be opioid-tolerant, defined as taking ≥60 mg/day of oral morphine or an equivalent dose of another opioid for ≥1 week. Females of childbearing potential were required to have a negative urine pregnancy test, to not be breast-feeding, and to be practicing a reliable form of contraception.

Patients were excluded from study participation if they had uncontrolled or rapidly escalating pain or painful erythema, edema, or ulcers under the tongue. Also excluded were patients with a history of or current major organ system impairment or disease, or other comorbid medical conditions that could exacerbate the risks of opioids (e.g., obstructive sleep apnea).

Study drugs

During the titration phase, the initial dose of fentanyl sublingual spray was determined based on the patient's prior experience with immediate-release fentanyl products. For fentanyl-naïve patients (i.e., those with no history of using a TIRF), fentanyl sublingual spray was initiated at the lowest possible dose (i.e., 100 μg). The starting dose for patients with a history of using TIRFs was based on the patient's previously tolerated dose of oral transmucosal fentanyl citrate (OTFC) or fentanyl buccal tablet (FBT). Patients currently using a TIRF for BTCP were eligible for study enrollment only after a 7-day washout period. Fentanyl sublingual spray was administered as a single 100-μL spray that contained 100-, 200-, 400-, 600-, or 800-μg doses of fentanyl; for the 1200- and 1600-μg dosages, two sprays of 600 or 800 μg were used, respectively.

Outcomes

Safety

The primary safety outcome was the assessment of AEs that occurred throughout the study, (including those experienced by patients who were withdrawn because of an AE) and the occurrence of serious AEs (SAEs). AEs were rated by study investigators for intensity (mild, moderate, or severe) and relationship to study medication (not related, possibly related, or probably related). Other safety measures monitored during the

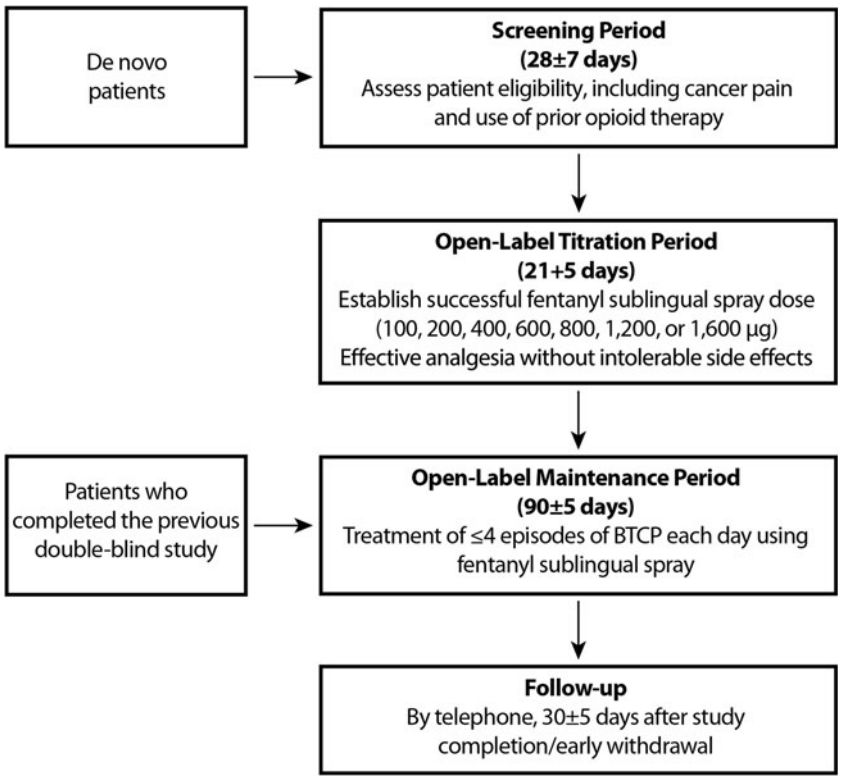

Fig. 1 Study design. *BTCP* breakthrough cancer pain

study included laboratory parameters (e.g., clinical chemistry, hematology), oral cavity examination, vital sign assessments, and electrocardiogram (ECG).

Patient satisfaction with medication

The Treatment Satisfaction Questionnaire for Medication (TSQM) [12] was administered before the first dose of fentanyl sublingual spray during the titration period, at the start of the maintenance period, and at each monthly visit until study completion or early termination. At the first assessment (before the first dose of fentanyl sublingual spray), patients were instructed to base their responses on the supplemental analgesic that they had usually been using for managing BTCP. At subsequent assessments, researchers instructed patients to base their responses only on fentanyl sublingual spray use. The TSQM includes four domains that measure different aspects of treatment satisfaction (i.e., effectiveness, side effects, convenience, and global satisfaction).

Statistical analysis

Descriptive statistics were used to summarize treatment-emergent AEs, other safety measures, and treatment satisfaction; because there was no comparator group, statistical comparisons were not performed. Laboratory parameters, ECGs, and oral examination findings were assessed for clinically meaningful changes from baseline. All missing data points were treated as missing, and no imputations were performed. Whenever possible, patients who discontinued before study completion were scheduled for an early withdrawal visit, where final safety and TSQM assessments were conducted.

The proposed population of 300 enrolled patients was selected to provide a population of 150 patients during the maintenance period that can be evaluated; this number was based upon the regulatory requirements, as opposed to being based on a statistical power calculation. This sample size provided 95 % certainty that an AE with ≥2 % probability would be observed in at least 1 patient.

Results

Patient disposition and baseline demographics

A total of 229 de novo patients were enrolled into the titration period, and 184 (80 %) patients completed the titration period (Fig. 2). Nearly all of the patients who discontinued during the titration period (43/45; 96 %) were withdrawn while receiving the lowest dose of fentanyl sublingual spray (i.e., 100 μg). The most common reasons for withdrawal of de novo patients were consent withdrawn (19/45; 42 %); occurrence of an AE that contraindicated further administration of the study drug (11/45; 24 %); and intercurrent illness, AE, or surgery (5/45; 11 %). Of the 184 patients who completed the titration period, 5 patients did not enter the maintenance period. Ninety (94.7 %) patients who had completed the double-blind study

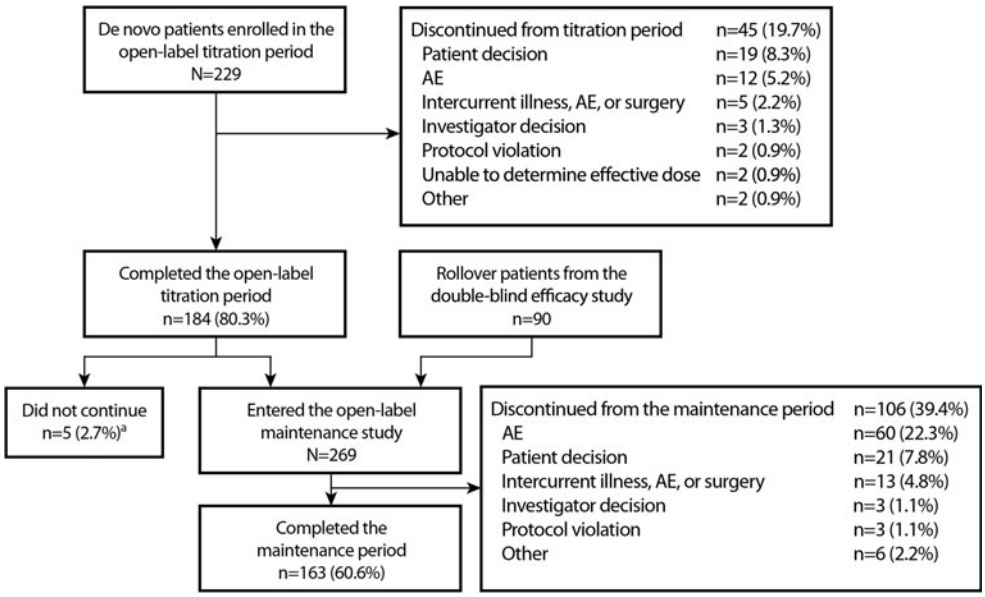

Fig. 2 Patient disposition. *AE* adverse event

agreed to roll over into the maintenance period of the long-term safety study. The completion rate for the 90-day maintenance period for the overall population (de novo and rollover patients) was 61 % (163/269).

Baseline patient demographic characteristics were similar for the populations enrolled in the titration and maintenance periods (Table 1). The population had a mean age of approximately 54 years, was evenly divided by sex, and primarily included patients who were white or Asian. Twenty-nine percent of the rollover patients (26/90) reported receiving chemotherapy, while all of the de novo patients had a history of chemotherapy use. Most of the de novo patients enrolled in the titration period reported that their persistent background pain during the past 24 h was mild to moderate in intensity; only 5 patients reported experiencing severe background pain and were included in the study. BTCP episodes in this patient population were generally rated as moderate in intensity; had a mean duration of approximately 60 min; occurred a mean of three times daily; and most commonly had a negative impact on walking, sleeping, and working. For the de novo population, overall mean time to pain relief with previous BTCP treatment was approximately 45 min of administration at baseline.

Table 1 Baseline demographics

Characteristic	Titration period ($N=229$)	Maintenance period ($N=269$)
Age, mean (SD), year	54.1 (12.5)	53.6 (12.2)
Sex, *n* (%)		
Female	117 (51.1)	141 (52.4)
Male	112 (48.9)	128 (47.6)
Race, *n* (%)		
White	135 (59.0)	178 (66.2)
Asian	81 (35.4)	75 (27.9)
Black or African American	7 (3.1)	10 (3.7)
Other	6 (2.6)	6 (2.2)
Ethnicity, *n* (%)		
Hispanic or Latino	6 (2.6)	8 (3.0)
Weight,[a] mean (SD), kg	67.1 (19.2)	71.8 (21.9)
Height,[a] mean (SD), cm	166.1 (11.7)	167.3 (11.9)
Body mass index,[a] mean (SD), kg/m^2	24.1 (5.9)	25.5 (7.0)

[a] Data were not available for all patients; $n=223$ to 226 in the titration period, $n=265$ to 267 in the maintenance period

Effective doses of fentanyl sublingual spray

Eighty percent of patients who entered the titration period were able to identify an effective dose of fentanyl sublingual spray. The median effective dose identified at the start of the maintenance period was 600 μg. A large percentage of patients (41 %) had an effective dose of fentanyl between 800 and 1600 μg. Average daily exposure to fentanyl sublingual spray during the maintenance period ranged from 140 to 9381 μg/day, depending on the effective dose used (Fig. 3).

Safety

Adverse events

A summary of AEs that occurred during the study by overall number, intensity, seriousness, and relation to study medication is presented in Table 2. The most commonly reported AEs observed during the titration period differed from those that were observed during the maintenance period (Table 3). Nausea (13 %), vomiting (12 %), and somnolence (10 %)

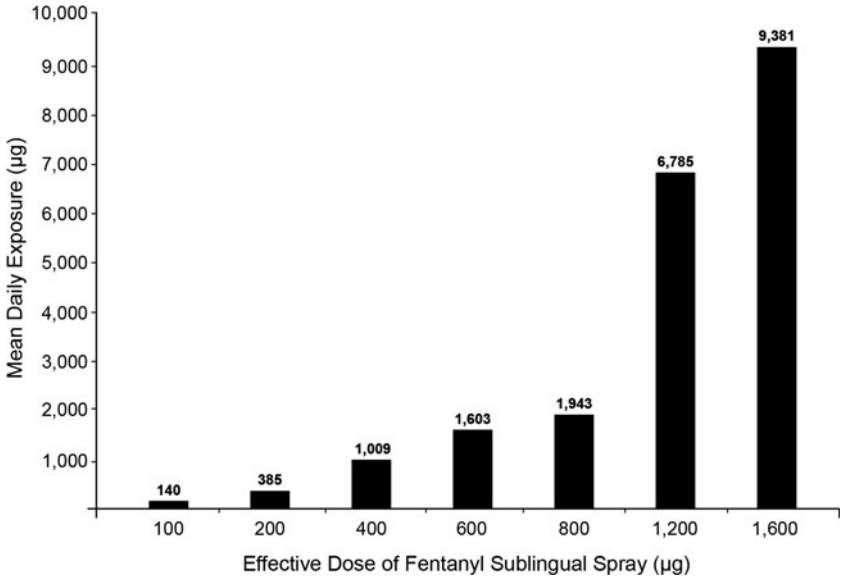

Fig. 3 Average daily exposure to fentanyl sublingual spray, by effective dose ($N = 269$)

were the most common AEs during the titration period, whereas malignant neoplasm progression (24 %), vomiting (16 %), and peripheral edema (12 %) were the most common AEs observed during the maintenance period. Most of the SAEs that were observed were related to the underlying disease (e.g., neoplasm or disease progression) and were not thought to be related to treatment with fentanyl sublingual spray by the investigators. Three patients experienced an SAE (other than death) during the maintenance period that was considered possibly related to study medication; these included diarrhea (1 patient), increased hepatic enzymes (1 patient), and general disorder or administration site condition events (1 patient). Eighty-nine deaths occurred overall; however, only one death, which was the result of asystole associated with cardiac arrhythmia, was considered possibly related to study medication. The other deaths were considered

Table 2 Summary of adverse events

AE category, *n* (%)	Titration period ($N = 229$)	Maintenance period ($N = 269$)
Patients with any AE	135 (59.0)	217 (80.7)
Patients with any AE, maximum intensity		
Mild	61 (26.6)	41 (15.2)
Moderate	49 (21.4)	57 (21.2)
Severe	25 (10.9)	119 (44.2)
Patients with an AE leading to withdrawal of study mediation	17 (7.4)	41 (15.2)
Patients with any SAE other than death	14 (6.1)	32 (11.9)
Deaths	10 (4.4)	79 (29.4)
AEs by relationship to study medication		
Not related	61 (26.6)	151 (56.1)
Possibly related	34 (14.8)	52 (19.3)
Probably related	40 (17.5)	14 (5.2)

AE adverse event, *SAE* serious adverse event

Table 3 Incidence of adverse events occurring in ≥5 % of patients in either study period

Titration period ($N = 229$)	
AE	Patients, *n* (%)
Nausea	30 (13.1)
Vomiting	27 (11.8)
Somnolence	23 (10.0)
Application-site irritation	17 (7.4)
Dizziness	16 (7.0)
Constipation	13 (5.7)
Maintenance period ($N = 269$)	
AE	Patients, *n* (%)
Malignant neoplasm progression	65 (24.2)
Vomiting	43 (16.0)
Peripheral edema	31 (11.5)
Constipation	28 (10.4)
Dyspnea	28 (10.4)
Nausea	28 (10.4)
Asthenia	26 (9.7)
Fatigue	23 (8.6)
Diarrhea	20 (7.4)
Pyrexia	18 (6.7)
Anemia	17 (6.3)
Cancer pain	17 (6.3)
Anxiety	16 (5.9)
Back pain	15 (5.6)
Anorexia	14 (5.2)
Cough	14 (5.2)
Dehydration	14 (5.2)

AE adverse event

not related to study medication and were most commonly due to the progression of the underlying cancer.

Other safety measures

During the titration and maintenance periods, laboratory values, vital signs, and physical examination findings generally remained within normal limits, or with minor changes from baseline. Shifts in liver enzymes from normal to elevated occurred in a small percentage of patients; these included alkaline phosphatase (13 %), lactate dehydrogenase (7 %), gamma-glutamyl transpeptidase (7 %), serum glutamic-pyruvic transaminase (6 %), and serum glutamic oxaloacetic transaminase (6 %); levels of the other liver enzymes that were measured were generally unchanged. A small percentage of patients also experienced shifts from normal to low levels of hematocrit (17 %), hemoglobin (14 %), and red blood cell count (14 %), which may be suggestive of anemia; some patients also reported anemia as an AE during the titration (1 %) and maintenance periods (6 %). No substantial changes in urinalysis or oral examination results were observed. There were no obvious changes in vital sign assessments; however, AEs related to vital signs such as pyrexia (titration, 5 %; maintenance, 7 %) and tachycardia (titration, 2 %; maintenance, 2 %) were observed.

Patient satisfaction with medication

On all domains of the TSQM, patients reported stable or improved levels of satisfaction from the start of the titration period (i.e., with their prior BTCP treatment) to the end of the maintenance period (i.e., with fentanyl sublingual spray). At the start of the titration period, 46 % of patients were satisfied, very satisfied, or extremely satisfied with the effectiveness of the supplemental analgesic they had typically been using to manage BTCP; this rate increased to a high of 87 % satisfaction with the effectiveness of fentanyl sublingual spray at the second maintenance period visit and was reported at 84 % at the final visit. When asked about how bothersome the side effects of their prior supplemental analgesic and fentanyl sublingual spray were, the percentage of patients who rated them somewhat, a little, or not at all bothersome remained relatively consistent between the titration period and the final visit (i.e., 77 and 76 %, respectively). However, more patients reported AEs associated with their previously utilized BTCP treatment (45 %) than with fentanyl sublingual spray (20–28 %). The percentage of patients who reported that their supplemental analgesic was convenient, very convenient, or extremely convenient was 77 % at the start of the titration period and rose to 87 % for fentanyl sublingual spray at the final visit of the maintenance period. The percentage of patients who rated global satisfaction with their current treatment as satisfied, very satisfied, or extremely satisfied was 50 % at the start of the titration period and 86 % at the final visit.

Discussion

During this study, fentanyl sublingual spray was associated with AEs that were consistent with what has been observed in patients receiving treatment with other strong opioids, and these AEs primarily involved the neurologic and gastrointestinal systems. The overall incidence of AEs appeared to be unrelated to the administered dose of fentanyl. In this study, an effective dose of fentanyl sublingual spray was identified for 80 % of patients who were enrolled in the titration period; for a majority of the patients, the effective dose was between 800 and 1600 μg. In addition, treatment satisfaction increased or remained stable from the start of the titration period (when patients were asked to rate their current BTCP analgesic) through the maintenance period (when they were asked to rate fentanyl sublingual spray), suggesting greater satisfaction with fentanyl sublingual spray in relation to the previously utilized BTCP treatment. This higher level of treatment satisfaction was maintained throughout the 90-day maintenance treatment period. The changes in laboratory values, vital sign assessments, and physical examinations are difficult to interpret given the number of patients who were undergoing chemotherapy for the treatment of cancer.

The AEs recorded in the current study were consistent with what has been observed in other long-term safety analyses conducted with orally administered TIRFs for managing BTCP [13–15]. In a study of 232 patients treated with FBT for BTCP, nausea, constipation, dizziness, and somnolence were the most commonly observed AEs during the maintenance phase [13]. Furthermore, in two other studies, patients with persistent cancer pain who were being treated with sublingual fentanyl orally disintegrating tablets most commonly experienced similar gastrointestinal (e.g., nausea, vomiting, constipation) and neurologic (e.g., somnolence, headache) AEs [14, 15].

Patient satisfaction with fentanyl sublingual spray observed in this study is consistent with what was reported in the pivotal, double-blind, efficacy study with fentanyl sublingual spray and with other orally administered TIRFs for managing BTCP [9, 13, 14, 16]. In addition, approximately 70 to 80 % of patients treated with FBT or sublingual fentanyl orally disintegrating tablet identified a successful dose [13, 14, 17], which is consistent with what was observed in the current study.

The primary limitation of this study is the lack of an inert or active comparator group, which would have allowed a clearer distinction to be made between safety issues that were related to treatment with fentanyl sublingual spray and those related to progression of the underlying cancer or its treatment.

In conclusion, in this long-term safety analysis, fentanyl sublingual spray was generally well tolerated for treating BTCP, and no new safety concerns were identified. In addition, patients reported a higher degree of satisfaction following initiation of treatment with fentanyl sublingual spray in comparison with their previously used BTCP treatment.

Acknowledgments Authors would like to acknowledge the following sites that participated in this study: Baylor Research Institute at Baylor All Saints Medical Center, Fort Worth, TX; Montana Cancer Institute Foundation, Missoula, MT; Coastal Orthopedics and Sports Medicine, Bradenton, FL; Four Seasons Hospice and Palliative Care; Flat Rock, NC; Samaritan Center for Medical Group Research Center; Los Gatos, CA; Aventura Research, Miami, FL; ResearchWest, Inc., Kalispell, MT; National Pain Research Institute, LLC, Winter Park, FL (also had a satellite site); Pain Consultants of Oregon, Eugene, OR; Henry M. Jackson Foundation, Brooke Army Medical Center, Ft Sam Houston, TX; Research Concepts, Ltd, Bellaire, TX; Clintell, Inc., Skokie, IL; Carolinas Pain Institute, P.A. & The Center for Clinical Research, Winston-Salem, NC; Loma Linda University Health Care; Center for Pain Management, Loma Linda, CA; Tennessee Valley Pain Consultants, Huntsville, AL; MAPS Applied Research Center, Minneapolis, MN; Center for Pain and Supportive Care, Phoenix, AZ; Allegheny Pain Management, PC, Altoona, PA; Gabrail Cancer Center, Canton, OH; Columbia Comprehensive Cancer Care Clinic, Jefferson City, MO; Dayton Science Institute; Dayton, OH; Northwest Regional Cancer Center, Winfield, AL; Wellmont Holston Valley, Kingsport, TN; Great Falls Clinic, Great Falls, MT; Geisinger Medical Center, Danville, PA; Fairview Southdale Medical Oncology, Edina, MN; Better Health Clinical Research, Newnan, GA; Hematology Oncology Associates, Lake Worth, FL; Midwestern Regional Medical Center, Zion, IL; Multicare Health System, Tacoma, WA; Central Pennsylvania Hematology and Medical Oncology Associates, PC, Lemoyne, PA; Newland Medical Associates, Southfield, MI; Fox Valley Hematology Oncology, Appleton, WI; Therapeutic Research Institute of Orange County, Laguna Hills, CA; Advanced Pain Consultants, PA, Voorhees, NJ; Indiana Medical Research, LLC, Elkhart, IN; Dallas Oncology Consultants, PA, Duncanville, TX; Center for Cancer & Blood Disorders, PC, Bethesda, MD; Palo Verde Hematology Oncology, Glendale, AZ; Chicago Research Center, Chicago, IL; Mills Peninsula Health Services, Dorothy Schneider Cancer Center, San Mateo, CA; Royal Victoria Hospital, Montreal, Quebec, Canada; St Paul's Hospital, Saskatoon, Saskatchewan, Canada; The Fe/Male Health Centers, Aurora, Ontario, Canada; CHUQ – CHUL, Quebec City, Quebec, Canada; Tata Memorial Hospital, Mumbai, Maharashtra, India; Bangalore Institute of Oncology, Bangalore, Karnataka, India; Kidwai Memorial Institute of Oncology, Bangalore, Karnataka, India; Samved Hospital, Navrangpura, Ahmedabad, Gujarat, India; Searoc Cancer Hospital, Jaipur, Rajasthan, India; Jawaharlal Nehru Cancer Hospital and Research Centre, Bhopal, Madhya Pradesh, India; Apollo Hospital, Hyderabad, Andhra Pradesh, India; Shatabdi Hospital, Nashik, Maharashtra, India; Kaushalya Medical Foundation Trust Hospital, Mumbai, Maharashtra, India; Deenanath Mangeshkar Hospital and Research Centre, Pune, Maharashtra, India.

Preliminary data were presented at the 31st Annual Scientific Meeting of the American Pain Society, May, 2012, Honolulu, HI. Technical editorial and medical writing assistance for the development of this manuscript was provided by Jonathan B. Kamien, PhD, for Synchrony Medical, LLC, West Chester, Pennsylvania. Funding for this support was provided by INSYS Therapeutics, Inc., Chandler, Arizona.

Compliance with ethical standards

Funding source This study was sponsored by INSYS Therapeutics, Inc.

Conflict of interest Dr Minkowitz has received clinical research funding from INSYS Therapeutics, Inc. Dr Bull has worked in a consultant/advisory role for INSYS Therapeutics, Inc. Dr Brownlow has no conflicts to disclose. Ms Parikh is a full-time employee of INSYS Therapeutics, Inc. Dr Rauck has worked in a consultant/advisory role for and received clinical research funding from BioDelivery Sciences International and INSYS Therapeutics, Inc.

Ethical approval This study was approved by the appropriate ethics committees, and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Informed consent All subjects provided informed consent prior to their inclusion in the study.

References

1. Portenoy RK, Payne D, Jacobsen P (1999) Breakthrough pain: characteristics and impact in patients with cancer pain. Pain 81:129–134
2. 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
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 Manage 20:87–92
5. Deandrea S, Corli O, Consonni D, Villani W, Greco MT, Apolone G (2014) Prevalence of breakthrough cancer pain: a systematic review and a pooled analysis of published literature. J Pain Symptom Manage 47:57–76
6. Zeppetella G (2010) Breakthrough cancer pain (BTcP): from definitions to patient burden. Eur J Palliat Care 17:4–7
7. Prommer E (2009) The role of fentanyl in cancer-related pain. J Palliat Med 12:947–954
8. Davis MP (2011) Fentanyl for breakthrough pain: a systematic review. Expert Rev Neurother 11:1197–1216
9. Rauck R, Reynolds L, Geach J et al (2012) Efficacy and safety of fentanyl sublingual spray for the treatment of breakthrough cancer pain: a randomized, double-blind, placebo-controlled study. Curr Med Res Opin 28:859–870
10. Subsys (fentanyl sublingual spray), CII [package insert]. Chandler, AZ: INSYS Therapeutics, Inc (2013)
11. Shojaei AH (1998) Buccal mucosa as a route for systemic drug delivery: a review. J Pharm Pharm Sci 1:15–30
12. Atkinson MJ, Sinha A, Hass SL et al (2004) Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. Health Qual Life Outcomes 2:12
13. 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
14. 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
15. Rauck RL, Tark M, Reyes E et al (2009) Efficacy and long-term tolerability of sublingual fentanyl orally disintegrating tablet in the treatment of breakthrough cancer pain. Curr Med Res Opin 25:2877–2885
16. Payne R, Coluzzi P, Hart L et al (2001) Long-term safety of oral transmucosal fentanyl citrate for breakthrough cancer pain. J Pain Symptom Manage 22:575–583
17. Nalamachu SR, Narayana A, Janka L (2011) Long-term dosing, safety, and tolerability of fentanyl buccal tablet in the management of noncancer-related breakthrough pain in opioid-tolerant patients. Curr Med Res Opin 27:751–760