



PRODUCT PROFILER

Abstral[®]

(Fentanyl Sublingual Tablets
For Breakthrough Cancer Pain)

Contents

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Trademark: P&T® is a registered trademark of MediMedia USA, Inc.

Publisher: P&T® is a peer-reviewed journal for managed care and hospital formulary management (ISSN 1052-1372) (GST #128741063) (IPM #0608025) and is published monthly by MediMedia USA, Inc., with business offices at 780 Township Line Road, Yardley, PA 19067; telephone: (267) 685-2788; fax: (267) 685-2966.

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POSTMASTER: Send address changes to P&T®, Box 2019, Langhorne, PA 19047. Periodicals postage paid at Morrisville Pa., and at additional mailing offices.

THE PRODUCT PROFILER

The Product Profiler provides P&T committee members with current, detailed information about a specific therapeutic agent to help them manage their formularies and establish medication-related policies. The Profiler provides information about pharmacology, clinical studies and FDA-approved indications, safety, efficacy, acquisition costs, and other pharmacoeconomic variables, along with additional P&T committee considerations, in a convenient package. Articles are written by experts in the field.

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In 2005, Dr. Chrvala founded Health Matters, Inc., to support the development of scientifically rigorous medical publications tailored to meet the unique informational and educational needs of physicians and other health care professionals. Current writing and research activities include manuscripts for peer-reviewed journals, continuing medical education, and summaries of key findings presented at professional conferences, advisory boards, and symposia. In addition, Dr. Chrvala also provides epidemiologic consulting services to a number of federal, state, and local health agencies, academic institutions, pharmaceutical companies, medical education organizations, and medical communication organizations.

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DISCLOSURES

Carole Alison Chrvala, PhD, and Alan Caspi, PhD, PharmD, MBA, both report that they have no financial arrangements or affiliations that might constitute a conflict of interest with respect to this publication. ProStrakan provided funding for this publication and had editorial control of its contents.



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INTRODUCTION

Pain is a significant and frequent consequence of cancer and one of the most feared symptoms associated with the diagnosis of cancer.^{1,2} Patients report that pain is associated with significant levels of physical discomfort, negative effects on their ability to engage in their usual activities, and diminished overall quality of life.¹ A meta-analysis of 52 studies calculated the pooled prevalence rates for cancer pain with results indicating that pain affected 33% of patients with newly diagnosed cancer (95% confidence interval [CI], 21%–46%), 59% of those undergoing therapy (95% CI, 44%–73%), 64% of patients with advanced disease (95% CI, 58%–69%), and 53% of patients with all stages of disease (95% CI, 43%–63%).²

Among 18 studies characterizing the severity of pain experienced by patients, more than one-third described their pain as moderate or severe.² Interviews conducted with 5,084 adults with cancer revealed that 56% of patients rated the intensity of their pain to be 5 or greater on a validated numerical rating scale (NRS) of 0 to 10 (where 0 = no pain and 10 = worst pain ever) and also reported several recurrent pain episodes in the past month.³ Notably, only 48% of adult patients with cancer-related pain reported good quality of life, whereas 51% indicated that pain interfered with their cognitive function, 69% reported disruptions in activities of daily living, 43% felt pain made them a burden on others for care, 30% experienced a level

of pain that prevented them from performing self-care activities, and 52% indicated diminished work performance.³ Emotional reactions to pain included feelings of distress (67%) and an intolerable aspect of having cancer (36%), with 32% of patients indicating that they experienced pain of such severity they felt they would rather die.³

The significant negative consequences of pain among cancer patients are a treatment priority for clinicians according to national and international guidelines.^{1,4} The World Health Organization (WHO) established an initial treatment algorithm for cancer pain management and recommended initiating treatment with acetaminophen or a nonsteroidal anti-inflammatory agent (NSAID), progressing to weak opioids for patients requiring additional relief, and the use of strong opioids (e.g., morphine) for pain not effectively controlled by milder agents.^{1,4} These guidelines have since been updated to more accurately reflect the complexities of effective pain management for patients with cancer.^{1,5–7} These updated guidelines include dosing recommendations for different classes of pharmacological agents (NSAIDs, opioids, and co-analgesics), frequently used to treat pain in cancer patients, as well as recommendations for titration and dose rotations, escalation of dosing, management of side effects, and alternative interventions for management of cancer pain.^{1,5–8}

Incidence and Severity of Breakthrough Cancer Pain

The clinical definition of breakthrough pain (BTP) refers to “transitory exacerbations of pain that occurs on a background of otherwise stable pain in a patient receiving chronic opioid therapy.”^{5,6,9–11} BTP is generally characterized by short, severe occurrences of pain uncontrolled by around-the-clock analgesics. Clinical definitions of BTP have been further refined by distinguishing between the following:^{5,6}

- *incident, predictable pain*: a consistent temporal causal relationship with a predictable motor activity such as movement, defecation, urination, or breathing
- *incident, unpredictable pain*: an inconsistent temporal causal relationship with predictable motor activity such as sneezing, bladder spasm, or coughing
- *idiopathic pain*: not associated with a known cause and usually of longer duration compared with incident pain
- *end-of-dose BTP*: pain occurring before a scheduled dose of an around-the-clock analgesic
- *procedural pain*: pain related to a therapeutic intervention such as dressing a wound

However, a recent systematic review of 51 papers concluded that currently there is no consensus for a definition of BTP. Furthermore, among 10 assessment tools commonly used to categorize BTP, none have been clinically validated. There are several methods of categorizing BTP in patients with cancer, although a formal classification system remains to be developed and validated.^{6,12} Despite limitations in the methods used to define, assess, and classify BTP, a number of studies have been conducted to assess the frequency, severity, duration, patterns, and predictors of BTP in patients with cancer.^{9–11,13,14}

Portenoy and colleagues conducted some of the earliest studies of BTP.^{10,11} Their findings suggest that BTP affected as many 63% of cancer patients at least once daily, with higher rates associated with precipitating events such as movement. There was wide variation in the number of BTP events, ranging from one event to 3,600 events, with a median of four BTP episodes occurring each day.¹⁰ The onset of BTP was rapid (within 3 minutes) for 43% of 51 BTP events, and the median duration of BTP was 30 minutes (range, 1–240 minutes).¹⁰ Importantly, all BTP events were characterized as severe or excruciating.¹⁰ Factors associated with the onset of BTP were identified for 55% of episodes and included end-of-dose failure plus a specific precipitant (12%), whereas 18% were a result of the end-of-dose alone; 43% had a pre-

cipitating event such as volitional movement (e.g., walking, coughing, sitting, standing, touching) or nonvolitional movement (bowel distention, ureter/renal distention, medication regurgitation).¹⁰

Among 164 patients with controlled background pain, 51.2% reported at least one BTP event per day with a median of six BTP events daily (range, 1–60); the median onset was 3 minutes (range, 1–30 minutes), and the median duration to peak intensity was 3.2 minutes (range, 1 second to 30 minutes).¹¹ Factors precipitating the onset of BTP were identified for 61.7% of events and included movement (20.4%), end-of-dose BTP (13.2%), and other events (28.1%).¹¹ The use of rescue opioid medications by patients with BTP was higher compared with patients who did not experience BTP (5.1 vs. 2.3 doses).¹¹

BTP was associated with significantly greater functional impairment, compared with background pain but no BTP episodes (24.8 vs. 16.7, $P < 0.001$).¹¹ Responses to the Brief Pain Inventory survey revealed that patients who experienced BTP reported a significantly greater negative impact of pain on their level of activity, mood, ability to walk, work performance, social relationships, sleep, and enjoyment of life, compared with patients who did not experience BTP ($P < 0.001$ for all comparisons).¹¹ Furthermore, BTP was also associated with higher levels of negative emotional reactions, including depression and anxiety, among patients with BTP compared with those who did not have BTP ($P < 0.01$ for both comparisons).¹¹ These results confirm the significant negative impact of BTP on functional status, emotional and psychological status, and overall quality of life among patients with cancer.¹¹

Mercadante and colleagues assessed the characteristics of BTP experienced by patients with cancer who were admitted to home-care programs or oncology units, as shown in Table 1.^{13,15} Among 101 patients treated in home-care settings and followed for three months, 70.2% were treated with analgesics upon admission; however, more than 50% had uncontrolled pain, including 39% experiencing moderate-to-severe pain and 49.2% reporting episodes of BTP with a mean intensity of 8 on a scale of 0 to 10 (the higher scores indicating more severe levels of pain).¹³

The mean duration of BTP episodes was 35.1 minutes, and patients reported a mean of 2.4 episodes of BTP per day.¹³ Precipitating factors included movement for 65.7% of BTP events, with a mean pain intensity score of 7.¹³

Treatment included no prescriptions for BTP medication for 67.7% of patients. The remaining patients received transmucosal fentanyl, oral morphine, tramadol, codeine, and non-opioid analgesics (see Table 1).¹³

Among 171 patients treated in oncology units, 87.1%

experienced BTP at baseline, which declined slightly to 80.9% at the third follow-up examination and 73.2% at the final six-month evaluation, although intensity of BTP did not decline during the follow-up interval.¹⁵ The duration of most BTP occurrences was less than 60 minutes, with four or fewer events per day reported by most patients.¹⁵

Treatment rates for BTP were much higher for patients in oncology units compared with those treated at home; 84.5% of patients receiving care in oncology units were prescribed medications for BTP at the baseline evaluation, but this rate decreased to 79% ($P = 0.033$) at the six-month follow-up examination.¹⁵ The primary pharmacological agents used to treat BTP were strong opioids for 55.5% of patients, including transmucosal fentanyl and oral morphine.¹⁵

Two prospective, longitudinal studies compared BTP characteristics, quality, and treatment for a racially and ethnically diverse sample of adults with cancer.^{9,14} Sig-

nificant racial and ethnic differences were evident for patient ratings of BTP severity, with non-Caucasian patients reporting more severe BTP intensity compared with Caucasians.^{9,14} Overall, BTP was associated with diminished functional quality of life, including general health, physical and role functions, and emotional, cognitive, and social functioning.¹⁴ Furthermore, patients who were representative of racial or ethnic minority groups reported higher rates of pain-related disability, depression, and post-traumatic stress disorder, compared with Caucasian patients, as well as lower quality of life.⁹

These studies and others confirm that BTP frequently affects patients with cancer and is characterized by an acute onset, a short duration, and moderate-to-severe intensity. BTP also has a significant negative impact on diverse functional domains, and there is generally poor overall pain control and management and low patient satisfaction with pain-management interventions.⁶

TABLE 1
Summary of Results from a Longitudinal Study of Breakthrough Pain (BTP) in Cancer Patients Admitted to Oncology Units

| | Assessment | | |
|--|-----------------------|-----------------------|-----------------------|
| | Baseline (N = 171) | 3 Months (N = 142) | 6 Months (N = 101) |
| BTP, n (%) | 149 (87.1) | 115 (80.9) | 74 (73.2) |
| <i>BTP intensity*, mean (SD)</i> | 6.7 (2.0) | 6.5 (1.8) | 6.5 (1.9) |
| <i>Duration, minutes, n (%)</i> | | | |
| • ≤ 30 | 85 (57.0) | 69 (60.0) | 46 (62.2) |
| • > 30–60 | 41 (27.5) | 30 (26.1) | 20 (27.0) |
| • 60–120 | 16 (10.7) | 7 (6.1) | 2 (2.7) |
| • > 120 | 7 (4.7) | 9 (7.8) | 6 (8.1) |
| <i>No. of episodes, n (%)</i> | | | |
| • 1 | 85 (57.0) | 65 (56.5) | 46 (62.2) |
| • 2–4 | 47 (31.5) | 45 (39.1) | 23 (31.1) |
| • > 4 | 17 (11.4) | 5 (4.3) | 5 (6.8) |
| BTP on movement, yes/no (%) | 65/149 (43.6) | 50/114 (43.4) | 24/74 (32.4) |
| <i>BTP intensity*, mean (SD)</i> | 7.2 (1.9) | 6.9 (1.6) | 6.8 (1.6) |
| <i>Duration of BTP with movement, minutes, n (%)</i> | | | |
| • ≤ 30 | 34 (52.3) | 28 (56.0) | 14 (58.3) |
| • > 30–60 | 18 (27.7) | 17 (34.0) | 10 (41.7) |
| • 60–120 | 10 (15.4) | 5 (10.0) | 0 (0.0) |
| • > 120 | 3 (4.6) | 0 (0.0) | 0 (0.0) |
| <i>Physical activity limitation †, n (%)</i> | | | |
| • 0 | 9 (13.8) | 2 (4.0) | 2 (8.3) |
| • 1 | 6 (9.2) | 5 (10.0) | 3 (12.5) |
| • 2 | 35 (53.8) | 35 (70.0) | 15 (62.5) |
| • 3 | 15 (23.1) | 8 (16.0) | 4 (16.7) |
| Satisfaction with analgesic treatment of BTP ‡, n (%) | | | |
| • 0 | 6 (4.8) | 3 (3.1) | 0 (0.0) |
| • 1 | 11 (8.7) | 7 (7.3) | 5 (8.5) |
| • 2 | 55 (43.7) | 42 (43.8) | 23 (39.0) |
| • 3 | 54 (42.9) | 44 (45.8) | 31 (52.5) |

*Rated on scale ranging from 0 to 10, with lower scores indicative of lower intensity.

† Graded as 0 = none, 1 = lightly, 2 = moderately, 3 = completely;

‡ Graded as 0 = none, 1 = poor, 2 = moderate, and 3 = good.

From Mercadante S, Zagonel V, Breda E, et al. *J Pain Symptom Manage* 2010;40:183190. (online, May 4, 2010.)¹⁵

Current Pharmacological Options And Treatment Guidelines

PATHOPHYSIOLOGY

Different types of pain are recognized among patients with cancer, including pain associated with the tumor, pain associated with treatment, and pain unrelated to either.¹ Distinguishing between acute and chronic pain is considered imperative in order to guide the proper choice of therapeutic interventions.¹ The pathophysiology of pain must be considered in the selection of therapy for cancer-related pain. There are two types of cancer-related pain: nociceptive and neuropathic.^{1,5}

Nociceptive pain is attributed to injury to somatic and visceral structures; this pain activates nociceptors present in skin, viscera, muscles, and connective tissue.¹ Nociceptive pain is further classified as visceral or somatic in nature. Somatic nociceptive pain presents as a sharp, well-localized, throbbing, and pressure-like sensation that frequently occurs after surgery or bone metastases.¹ Visceral nociceptive pain is characterized as more diffuse, aching, and cramping and is attributed to compression, infiltration, or distention of the abdominal thoracic viscera.¹

Neuropathic pain occurs in response to injury to the peripheral or central nervous system and is frequently described as burning and sharp.¹ Neuropathic pain affecting patients with cancer can result from spinal stenosis, neuropathy, or an adverse effect of chemotherapy or radiation therapy.¹

TREATMENT GUIDELINES

Various guidelines recommend the following steps to ensure optimal pain management for patients with cancer-related pain.^{1,5,6}

1. A formal, comprehensive pain assessment should be conducted at a patient's initial evaluation, at regular follow-up intervals, and when new therapies are initiated.

2. Comprehensive pain assessments should characterize the type and quality of pain; the onset, duration, course, and intensity of pain; factors that provoke or relieve pain; current pain-management strategies; the effectiveness of these interventions; and psychosocial factors (e.g., the patient's emotional state, availability of social support, psychiatric history, risk for abuse of pain medications, and risk factors for undertreatment of pain).

3. Quantification of pain intensity by the patient with a numerical value, categorical scale, or pictorial scale to describe the severity of pain.

The NCCN guidelines define mild pain intensity as 1 to 3 on a 0 to 10 numerical scale, 4 to 6 for moderate pain, and 7 to 10 as severe pain.¹ The guidelines also distinguish between pain attributed to oncologic emergencies, patients who are opioid-naïve, and patients who are opioid-tolerant.¹ Opioid-tolerant patients include those taking at least oral morphine 60 mg/day, transdermal fentanyl 25 mcg/hour, oxycodone 30 mg/day, hydromorphone 8 mg/day, oral oxymorphone 25 mg/day, or an equianalgesic dose of another opioid for one week or longer.¹

The general principles for selection of an appropriate dose of opioids should rely on an individualized approach based on pain intensity, current analgesic therapy, and comorbid health conditions.^{1,6,7} The most commonly used opioids in the U.S. are morphine, hydromorphone, fentanyl, and oxycodone, with the goal of providing optimal pain relief and minimal side effects through careful selection of the starting dose, frequency, and upward dose titration.^{1,6,7} It is also recommended that the route of administration be the least invasive, easiest, and safest while ensuring satisfactory pain relief.^{1,6,7} European Society for Medical Oncology (ESMO) guidelines recommend oral morphine for severe pain, with the parenteral dosage reduced to one-third of the oral dose.⁸ An alternative to oral morphine includes hydromorphone or oxycodone (normal and modified-release for oral use) and transdermal fentanyl for patients with stable opioid requirements.⁸

Opioid-tolerant patients experiencing BTP with a pain intensity score of 4 or higher, or a pain intensity score of less than 4 but inadequate pain control, require regular supplemental doses of opioids; efficacy and safety should be regularly assessed for both oral and parenteral agents, including consideration of transmucosal fentanyl.¹ Opioids used for the management of BTP should provide a rapid onset of analgesic action of duration appropriate for the characteristics of the BTP episodes.^{6,7}

Oral morphine, hydromorphone, and oxycodone are among the most frequently used agents for BTP, but they require approximately 30 to 40 minutes for relief because of their first-pass effect and hydrophilic formulation, which slows absorption from the gastrointestinal (GI) tract. These oral agents are also associated with variabilities in therapeutic effect.^{6,7,16}

Fentanyl is well suited for absorption through the oral mucosa, is generally associated with low levels of local irritation, and offers more rapid onset of relief compared with opioids given through alternative routes such as oral and rectal administration.^{6,7,17} Some formulations of oral

fentanyl, however, do provoke application-site reactions for as many as 10% of patients, such as paresthesia, ulceration, and bleeding.¹⁸ Four percent of patients reported pain, 3% reported ulcers, and 3% reported local irritation in response to fentanyl buccal tablets.¹⁸

PHARMACOTHERAPY TAILORED TO MANAGE THE CHALLENGE OF BREAKTHROUGH PAIN

Optimal management of BTP experienced by patients with cancer requires a rapid assessment of the pharmacological effects of medications, given the sudden onset, severity, and frequency of BTP episodes (Figure 1 and Table 2).^{5–7,20,21} Parenteral administration accomplishes the goal of rapid onset of pain relief but compromises patient convenience and might not be feasible for some patients because of severe, generalized, massive edema (anasarca) coagulopathy, compromised circulatory system, and patient or caregiver reluctance to accept the discomfort and invasiveness associated with parenteral administration.^{7,16,20,22} Therefore, alternative routes of administration that do not compromise efficacy and safety are a priority for patients requiring rapid relief of moderate-to-severe BTP episodes.

The imperative for this type of formulation has prompted efforts to develop new, nonparenteral, reliable, and convenient forms using routes of administration that promote rapid absorption of the drug into systemic circulation.^{20,22} Tablet formulations offer the advantages of easy production and are simple to take by patients, or they can be administered by lay caregivers.²² However, conventional tablets have a delayed onset of action because of the lag time between ingestion and intestinal absorption; it is estimated that it takes up to 30 minutes for the onset of analgesia following oral opioid administration.^{20,22} This results, in part, from delayed absorption of the medication in the GI tract.

New formulations of rapidly absorbed sublingual tablets offer a promising alternative for delivering effective pharmacological treatment of BTP.^{20,22} These formulations are based on the use of ordered mixtures of fine-drug particles that are attached to coarser excipient carrier particles.²² The ordered mixtures facilitate development of tablets that dissolve rapidly, result in optimal drug exposure, and have the potential to provide immediate drug dissolution.²² Furthermore, the addition of small bioadhesive units to the surface of carrier particles results in ordered units of medication that consist of coarse particles carrying both the bioadhesive component and the drug.²² This formulation promotes rapid disintegration and release of the carrier units that adhere to the sublingual mucosa.²² Drugs that dissolve instantly and permeate the

mucous membranes are rapidly absorbed before being swallowed.²² The highly vascularized oral mucosa allows direct entry of the drug into systemic circulation, eliminating the need for passage through the GI system and the liver.^{20,22}

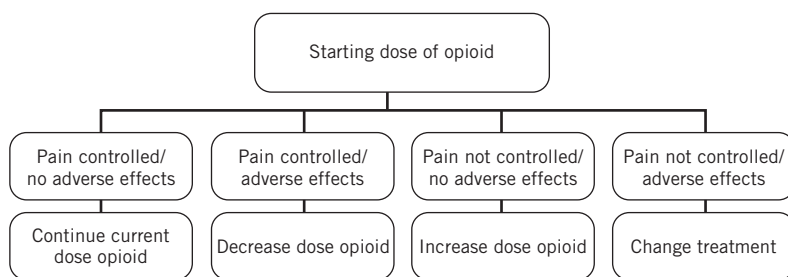
The short disintegration and dissolution times are among the most important features of sublingual formulations of drugs intended for oromucosal delivery.^{7,16,20,22} More rapid absorption of sublingual agents is likely to result in faster time to achieve analgesic effects.^{7,16,20}

Additional advantages of sublingual formulations include simplicity of administration by patients and caregivers, lower cost, and use of a noninvasive route that does not provoke discomfort, such as that caused by parenteral administration.²⁰

Sublingual agents also provide alternatives when oral routes are not available because of obstructive GI tract tumors, dysphagia, odynophagia, nausea and vomiting, and loss of consciousness at the end of life.^{16,20} Possible limitations of sublingual drug administration include an unacceptable taste; a burning sensation; rare events of ulceration of the oral mucosa, which is a particular concern for patients with dysphagia; treatment-related mucositis; oral candidiasis; xerostomia; and the need to retain the drug under the tongue for several minutes.^{16,20}

Fentanyl is a synthetic opioid used for the treatment of BTP; its potency results from its rapid onset of action.^{20,22,23} Efforts to develop and evaluate the efficacy and safety of a sublingual solid dose formulation of fentanyl for BTP have been motivated by the need to provide rapid and reproducible onset of pain relief that is convenient for patients to use.²² Sublingual formulations of fentanyl increase retention of the active substance under the tongue, increase optimal exposure of the active agent to dissolving fluids at the absorption site, avoid the risk of swallowing that is associated with inter-individual variability in efficacy, and bypass GI and hepatic metabolism.^{22,23} Sublingual formulations of oral fentanyl offer the advantage of low rates of oral adverse events (AEs), which

FIGURE 1
Dose-titration scheme for opioid rescue medication for breakthrough pain



From Davies AN, Dickman A, Reid C, et al. *Eur J Pain* 2009;13(4):331–338.⁶

TABLE 2
Summary of Recommendations for Management of Breakthrough Pain in Patients with Cancer

| Recommendation | Recommendation Grade* |
|--|-----------------------|
| Patients with pain should be assessed for the presence of BTP | D* |
| Patients with BTP should have this pain specifically assessed | D† |
| Management of BTP should be individualized | D |
| Consider treatment of the underlying cause of the pain | D |
| Consider strategies to avoid or treat precipitating factors associated with BTP episodes | D |
| Consider modification of background analgesic regimen/“around-the-clock medication” | D |
| Opioids are the rescue medication of choice for BTP episodes | D |
| Dose of opioid rescue medication should be determined by individual titration | B |
| Consider non-pharmacologic treatments for management of BTP episodes | D |
| Non-opioid analgesics may be useful for management of BTP episodes | D |
| Interventional techniques may be useful for management of BTP episodes | D |
| Specifically reassess BTP at periodic intervals | D |

* D = extrapolated evidence from well-conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal or nonanalytic studies such as case reports or case series or expert opinion.

† B = body of evidence from high quality systematic reviews of case-control or cohort studies or high-quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal or extrapolated evidence from studies that are high quality meta-analyses, systematic reviews of randomized, controlled trials (RCTs) or RCTs with a very low risk of bias or well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with low risk of bias (Harbour R, Miller J. *BMJ* 2001;323(7308):334–336²⁰).

From Davies AN, Dickman A, Reid C, et al. *Eur J Pain* 2009;13(4):331–338.⁶

is a particular concern for patients with dysphagia, treatment-related mucositis, candidiasis, or xerostomia.^{7,16} Fentanyl buccal tablets (Fentora) result in application-site reactions in 10% of patients.¹⁸

Fentanyl sublingual tablets (FST, or Abstral) have not been found to have the bitter taste associated with other opioids.²³ Although most patients reported some taste and/or aftertaste related to FST, patients in a 2010 study determined that the taste was not stronger than “mild” in intensity, and all patients in the study indicated that they would be willing to continue FST treatment over the long term.²⁴ This is discussed further below.

Studies have examined rates of disintegration and dissolution of FST, and their relationship to rates of absorption and decreased risk of swallowing the active ingredient.^{22,23} In one trial, plasma concentrations of fentanyl were achieved within 10 minutes of intake after a single dose. With FST, the exposure of the active substance to the dissolving fluids in the mouth is combined with bioadhesive retention of the drug in the oral cavity, resulting in rapid sublingual absorption.²²

Similarly, in an evaluation of single doses of FST 100, 200, and 400 mcg administered to patients with cancer, plasma area-under-the-curve (AUC) and peak (C_{max}) levels linearly increased with the dose, and plasma concentrations achieved the established therapeutic range for fentanyl.²³ The time to the first detectable concentration (t_{max}) of drug in plasma ranged from 8 to 11 minutes for all three doses. There was little inter-individual variability in systemic exposure, and the formulation was well tolerated, with few adverse events (AEs) beyond what is typically seen with opioid medications.²³

Other sublingual fentanyl products have different delivery systems that might make patient compliance more difficult to achieve. For example, fentanyl buccal tablets (Fentora) must be left in place for 14 to 25 minutes until

the tablet is dissolved¹⁸, and with the fentanyl citrate oral transmucosal lozenge (Actiq) unit, patients must move the drug around in the mouth and twirl the handle often, for a period of 15 minutes.¹⁹

A phase 1, open-label, single-dose study evaluated the pharmacokinetics and tolerability of FST administered in four doses (50, 100, 150, and 200 mcg).²⁵ Plasma concentrations of fentanyl increased with the dose, and absorption was rapid, based on t_{first} (range, 15 minutes for the 50-mcg dose to 10.2 minutes for the other three doses for all patients) and t_{max} (range, 45 minutes for the 50- and 200-mcg doses and 30 minutes for the 100- and 150-mcg doses).²⁵ All AEs were mild to moderate. Somnolence was reported as the most common event, although the rate of AEs increased with ascending doses of FST.²⁵ A comparison of responses to FST among patients of diverse ethnicity (Caucasian and Japanese) revealed no significant differences in kinetics, suggesting that there is no need for dose modification based on ethnicity.²⁵

A phase 1 pharmacokinetic study was conducted to determine the acceptability of FST for the treatment of breakthrough cancer pain.²³ Three doses of FST were administered to 11 opioid-tolerant patients with cancer on separate days with a one-day separation between each of the three doses.²³ Dosing was with FST 100 mcg, 200 mcg, and 400 mcg.²³ Patients completed a brief questionnaire to assess acceptability of the formulation, including questions about the taste and pleasantness of the agent; the nature and strength of a sweet, sour, bitter, or salty taste; a tendency to gag or vomit following use; any aftertaste; and their willingness to use FST over the long term.²⁴

Eighty-five percent of patients indicated that FST was tasteless or virtually tasteless and acceptable. Evaluations of a sweet, sour, bitter, or salty taste revealed that 29% of patients rated the formulation as tasteless, with the

majority of other responses indicating a moderately sweet taste.²⁴ No patients reported gagging associated with FST, and 60% indicated the absence of any aftertaste. Among patients (40%) who reported an aftertaste, the maximum intensity was mild, with the duration ranging from 1 to 30 minutes.

Among a total of 27 evaluations provided by the 11 study participants, 100% indicated they would be willing to take FST over the long term.²⁴ These results support the

acceptability of FST to patients for the long-term treatment of breakthrough cancer pain.

Results from these studies have established that the potency, lipophilicity, efficacy, and a favorable side-effect profile of FST make it a preferred choice of an analgesic for the treatment of BTP in patients with cancer.^{7,20}

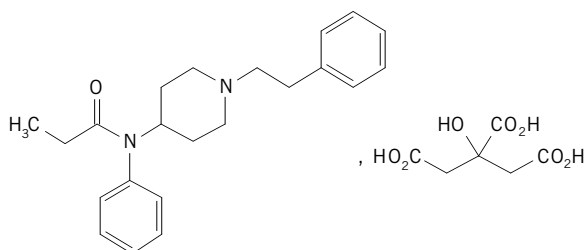
Additional clinical trials of FST are discussed in greater detail beginning on page 11.

Chemistry and Pharmacokinetics

CHEMICAL AND PHYSICAL PROPERTIES²⁶

Abstral (fentanyl sublingual tablets, or FST) is a solid formulation of fentanyl citrate, a potent opioid analgesic intended for oral sublingual administration. FST is formulated as a white tablet available in six strengths. It is distinguishable by the shape of the tablet and by debossing on the tablet's surface.

The active ingredient is fentanyl citrate, USP is *N*-(1-phenethyl-4-piperidyl) propionanilide citrate (1:1). Fentanyl is a highly lipophilic compound (octanol–water partition coefficient at pH 7.4 is 816:1) that is freely soluble in organic solvents and sparingly soluble in water (1:40). The molecular weight of the free base is 336.5 (the citrate salt is 528.6). The pKa of the tertiary nitrogens are 7.3 and 8.4. The compound has the following structural formula:



All tablet strengths are expressed as the amount of fentanyl free base (e.g., the 100-mcg strength tablet contains 100 mcg of fentanyl free base).

Inactive ingredients include croscarmellose sodium, magnesium stearate, mannitol, and silicified microcrystalline cellulose.

MECHANISM OF ACTION AND CLINICAL PHARMACOLOGY²⁶

Fentanyl is a pure opioid agonist whose principal therapeutic action is analgesia. Other members of the class known as opioid agonists include substances such as morphine, oxycodone, hydromorphone, codeine, and hydrocodone.

Pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, cough suppression, and analgesia. Like all pure opioid agonist analgesics, with increasing doses there is increasing analgesia; by contrast, mixed agonist/antagonists or non-opioid analgesics have a limited analgesic effect with increasing doses. With pure opioid agonist analgesics, there is no defined maximum dose; the ceiling to analgesic effectiveness is imposed only by side effects, the more serious of which may

include somnolence and respiratory depression.

The analgesic effects of fentanyl are related to the blood level of the drug if proper allowance is made for the delay into and out of the central nervous system (CNS), a process with a 3- to 5-minute half-life. In general, the effective concentration and the concentration at which toxicity occurs increase with increasing tolerance with any and all opioids. The rate of development of tolerance varies widely among individuals. As a result, the dose should be titrated to achieve the desired effect.

Central Nervous System. The precise mechanism of the analgesic action is unknown, although fentanyl is known to be a mu-opioid receptor agonist. Specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and play a role in the analgesic effects of this drug.

Fentanyl produces respiratory depression by direct action on brain stem respiratory centers. Respiratory depression involves a reduction in the responsiveness of the brain stem both to increases in carbon dioxide and to electrical stimulation.

Fentanyl causes miosis even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic. For example, pontine lesions of hemorrhagic or ischemic origin may produce similar findings.

Gastrointestinal System. Fentanyl causes reduced motility associated with an increase in smooth-muscle tone in the antrum of the stomach and in the duodenum. Digestion of food is delayed in the small intestine, and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, whereas tone may be increased to the point of spasm, resulting in constipation. Other opioid induced-effects may include a reduction in gastric, biliary, and pancreatic secretions; spasm of the sphincter of Oddi; and transient elevations in serum amylase.

Cardiovascular System. Fentanyl may produce the release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Endocrine System. Opioid agonists have been shown to have a variety of effects on the secretion of hormones. Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin secretion, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon in humans and other species (e.g., in rats and dogs). Thyroid stimulating hormone (TSH) is

both inhibited and stimulated by opioids.

Respiratory System. All opioid mu-receptor agonists, including fentanyl, produce dose-dependent respiratory depression. The risk of respiratory depression is lower in patients receiving chronic opioid therapy who develop tolerance to these effects. Peak respiratory depressive effects may be seen as early as 15 to 30 minutes from the start of oral transmucosal fentanyl citrate administration and may persist for several hours.

Serious or fatal respiratory depression can occur even at recommended doses. Fentanyl depresses the cough reflex as a result of its CNS activity. Although not observed with oral transmucosal fentanyl products in clinical trials, fentanyl given rapidly by intravenous (IV) injection in large doses may cause rigidity in the muscles of respiration, resulting in respiratory difficulties. Therefore, prescribers should be aware of this potential complication.

PHARMACOKINETICS AND DRUG METABOLISM²⁶

Absorption

Fentanyl is a highly lipophilic drug. Orally administered fentanyl undergoes pronounced hepatic and intestinal first-pass effects. Absorption of fentanyl from FST is mainly through the oral mucosa.

The bioavailability of FST has been calculated to be 54%.

Dose proportionality across the 100- to 800-mcg dose range has been demonstrated. The median time to maximum plasma concentration (T_{max}) across four doses of FST varied from 30 to 60 minutes (range, 15–240 minutes). In another study, dose proportionality between 800

mcg and 1,600 mcg in C_{max} and AUC has also been demonstrated.

Pharmacokinetic studies have shown that multiple tablets are bioequivalent to single tablets of the equivalent dose.

Distribution

Fentanyl is highly lipophilic. Animal data showed that following absorption, fentanyl is rapidly distributed to the brain, heart, lungs, kidneys and spleen followed by a slower redistribution to muscles and fat. The plasma protein binding of fentanyl is 80% to 85%. The main binding protein is alpha-1-acid glycoprotein, but both albumin and lipoproteins contribute to some extent. The free fraction of fentanyl increases with acidosis. The mean volume of distribution at steady state (V_{ss}) was 4 L/kg.

Metabolism and Excretion

Fentanyl is metabolized in the liver and in the intestinal mucosa to norfentanyl by cytochrome P450 3A4 isoform. Norfentanyl was not found to be pharmacologically active in animal studies.

Elimination

Fentanyl is more than 90% eliminated by biotransformation to *N*-dealkylated and hydroxylated inactive metabolites. Less than 7% of the dose is excreted unchanged in the urine, and only about 1% is excreted unchanged in the feces. The metabolites are mainly excreted in the urine, while fecal excretion is less important. The total plasma clearance of fentanyl was 0.5 L/hour per kg (range, 0.3–0.7 L/hour per kg).

Clinical Trials

Randomized Phase 2 Study of the Efficacy and Tolerability of Sublingual Fentanyl For Cancer Patients with Breakthrough Pain

Overview of Trial Design and Objectives²⁷

A small, proof-of-concept study, conducted by Lennernäs et al., was designed as a randomized, multicenter, double-blind, four-period, cross-over trial. The study's objective was to evaluate the efficacy and tolerability of fentanyl sublingual tablets (FST, Abstral), administered in doses of 100, 200, or 400 mcg for the treatment of breakthrough pain (BTP) in opioid-tolerant patients with locally advanced or generalized cancer. Participating clinical centers included five university clinics in Sweden. The study was completed between July 2002 and January 2004. The study design did not include a dose-titration period, which precluded determination of the most effective and tolerable dose for each patient.

Methods²⁷

Eligible patients included those who were (1) male or female, (2) 18 to 90 years of age, (3) had locally advanced or metastatic cancer, (4) regularly experiencing four or more episodes of BTP over two weeks, and (5) currently receiving a fixed-schedule dose of opioids equal to oral morphine 30 to 1,000 mg/day or transdermal fentanyl 25 to 300 mcg/hour (Figure 2). Study exclusion criteria included any clinical or laboratory signs of any organ disease or progressive cancer that could interfere with study participation, use of any other investigational drugs in the eight weeks preceding screening for trial enrollment, a history of intolerance to fentanyl, severe allergic disease, and a history of drug abuse. All patients had the option to discontinue study participation at any time. The occurrence of unacceptable AEs, failure to adhere to the study protocol, or failure to attend study follow-up visits prompted cessation of study participation.

A single 14-day screening period was conducted for each patient during which patients

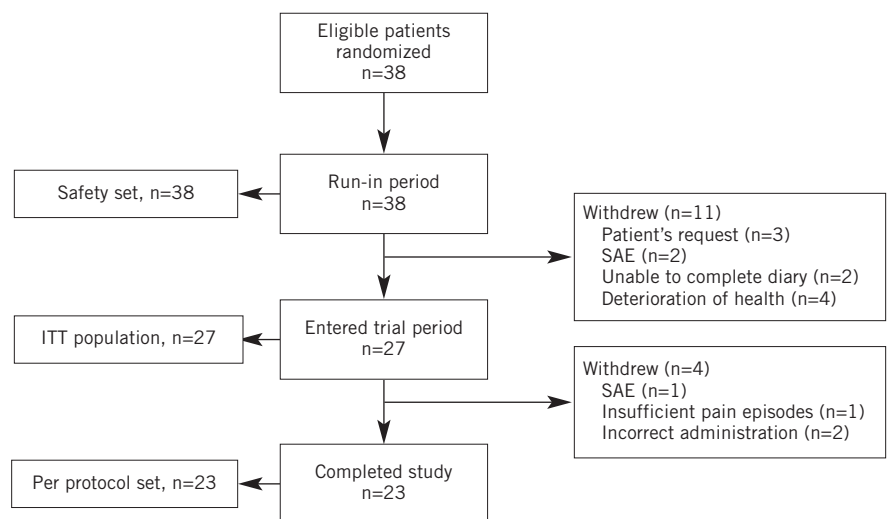
underwent a full clinical screening before randomization to FST or placebo. In addition, the nature and severity of BTP and need for rescue medication was assessed with patients rating their pain on a 100-mm Visual Analogue Scale (VAS) ranging from 0 (no pain) to 100 (worst conceivable pain) immediately prior to receiving their rescue dose of pain medication. Patients were also required to provide a global evaluation of their treatment and record their need for opioid therapy during a minimum of four episodes of acute pain.

The study drug was administered at the randomization visit, and patients received a single dose of placebo or FST 100, 200, or 400 mcg in random order at four pain episodes that occurred during the treatment periods. There was no effort to complete a dose-titration interval. Consequently, not all patients received an optimal dose of FST. Each treatment period was separated by a minimum of one-day washout period. All patients received one of each of the three doses of FST and placebo in a blinded, randomized manner.

Study Assessments: Efficacy and Safety²⁷

The primary measure of efficacy was patient ratings of pain intensity difference (PID) before and after taking each dose of medication according to the 100-mm VAS.

FIGURE 2
Patient disposition



ITT = intent-to-treat; SAE = serious adverse event.

From Lennernäs B, Frank-Lissbrant I, Lennernäs H, et al. *Palliat Med* 2010;24[3]:286–293.²⁷

The intensity of BTP was scored immediately before each dose of medication was taken and at 5, 10, 15, 20, and 30 minutes following treatment. Secondary efficacy measures included:

- global assessment of treatment indicated on a 4-point scale (none, mild, moderate, or excellent) recorded at 60 minutes following administration of study drug as a composite of study drug and rescue medication effectiveness for relief of BTP.
- the need for rescue medication recorded by patients in patient diary with rescue medications given 30 minutes after a dose of the study drug was taken.

Each primary and secondary efficacy variable was assessed for each of the four BTP events.

Safety assessments included AEs and laboratory assessments. AEs were evaluated at the time of randomization and post-study as well as between the two study visits. A safety evaluation visit occurred two to 10 days after administration of the final dose of the study medication and included a physical examination and laboratory evaluations. Patients with laboratory values exceeding reference values that were considered clinically significant were excluded from the study or withdrawn. Laboratory assessment changes that differed from baseline, in the opinion of the investigators, were considered AEs.

The statistical analysis plan included descriptive statistics, paired *t*-tests to compare differences between placebo and the three doses of FST, and tests for linear trends for treatment, pain episode, and time in a two-tail model. The intention-to-treat (ITT) analysis was a maximum-likelihood, random-intercept model that compared mean PID as the dependent variable per episode by episode and treatment using a random-effects model, whereas a mixed-effects model tested treatment and time interactions with PID as the dependent variable. All analyses were performed with SAS software (SAS Institute Inc., Cary, N.C.)

Results²⁷

The study included 38 patients, with 57.9% men, ranging from 40 to 80 years of age with a mean age of 63 years. All patients were Caucasian (Table 3). Among enrolled patients, 23 of 38 (60.5%) completed all four treatment doses and these comprised the per-protocol-set (PPS) of patients for analysis. A total of 27 of the 38 enrolled patients received at least one dose of the study drug, and these patients comprised the ITT population. A total of 101 single doses of FST were administered to patients during the study. All 38 patients were included in the safety analysis, including 15 who did not complete the study. Reasons for study discontinuation included inability to complete the patient diary, incorrect administration of study drug, an inadequate number of pain events, declines in medical status, serious AEs, and death.

A total of 121 pain episodes were treated during the

TABLE 3
Baseline Characteristics of the Study Population

| Characteristic | All Randomized Patients (N = 38) | Per-Protocol Patients (n = 23) |
|--------------------------|----------------------------------|--------------------------------|
| Sex, n (%) | | |
| • Female | 16 (42.1) | 10 (43.5) |
| • Male | 22 (57.9) | 13 (56.5) |
| Age, mean, years (range) | | |
| • Female | 61 (46–80) | 63 (46–80) |
| • Male | 65 (40–78) | 65 (40–74) |
| Race, n (%) | | |
| • Caucasian | 38 (100) | 23 (100) |

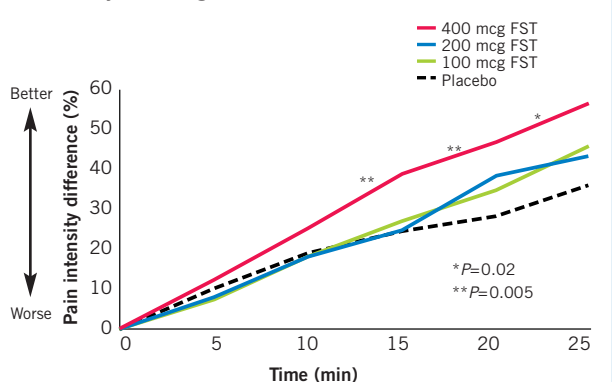
From Lennernäs B, Frank-Lissbrant I, Lennernäs H, et al. *Palliat Med* 2010;24(3):286–293.²⁷

run-in phase, with a mean of 5.3 events per patient. The mean dose of opioids during the run-in phase was 144.8 mg (range, 50–600 mg) and the mean dose of rescue medication was 29.6 mg (range, 5–150 mg).

Efficacy results. Among patients in the PPS population, 22 of 23 (95.7%) reported at least one dose of FST that achieved a clinically meaningful reduction in pain intensity (more than a 20-mm decrease on the VAS). There was a significant overall improvement in PID for FST 400 mcg compared with placebo (8.57 mm; *P* < 0.001). A statistically significant effect of FST 400 mcg was evident at 15 minutes following administration (Figure 3) (*P* = 0.005). Nonstatistically significant trends for improvement in PID were evident for the two lower doses of FST (*P* = 0.137 and 0.402 for FST 100 and 200 mcg, respectively).

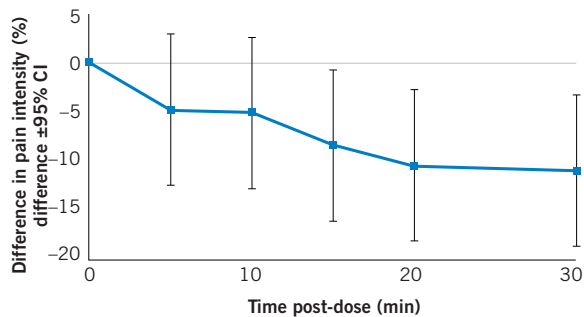
The analysis of the ITT population revealed significant improvements in pain control for FST 400 mcg versus placebo (*P* = 0.007). Pain relief with FST 400 mcg was

FIGURE 3
Mean pain intensity differences by time and dose of fentanyl sublingual tablets (FST)



Adapted from Lennernäs B, Frank-Lissbrant I, Lennernäs H, et al. *Palliat Med* 2010;24(3):286–293.²⁷

FIGURE 4
Differences in pain intensity between fentanyl sublingual tablets 400 mcg and placebo



Vertical bars indicate 95% confidence interval (CI).
Adapted from Lennernäs B, Frank-Lissbrant I, Lennernäs H, et al. *Palliat Med* 2010;24(3):286–293.²⁷

evident at five minutes post-dose and continued to improve with time (Figure 4). The evaluation of the overall effect of FST (all three doses combined), compared with placebo, revealed statistically significant improvements in pain control ($P = 0.027$); most of this effect was attributed to the 400-mg dose.

Analysis of the secondary efficacy measures revealed significantly greater effectiveness of FST 400 mcg, compared with placebo, on the global assessment of treatment (nine patients treated with FST 400 mcg vs. three in

the placebo group). The need for rescue medication was also significantly lower for patients who received FST 400 mcg compared with placebo (5 vs. 15 patients; $P = 0.001$), with 11 and 10 patients treated with FST 100 mcg and 200 mcg, respectively, requiring rescue medications, compared with 15 patients in the placebo group.

Safety results. AEs were reported by 13 patients, for a total of 15 events. The most frequent AEs were pain (in four patients) and vomiting (in two patients) (Table 4). In addition, two events that were considered to be related to the study drug were reported for patients receiving FST 400 mcg within 30 to 60 minutes following administration. These were classified as moderate-severity nausea and vomiting and mild-severity dizziness. There was no evidence of significant differences in the total number of AEs between the three doses of FST.

Randomized Phase 3 Study of the Efficacy and Long-Term Tolerability of Sublingual Fentanyl For Cancer Patients with Breakthrough Pain

Overview of Trial Design and Objectives¹⁷

A study was conducted by Rauck et al. to evaluate the efficacy and long-term tolerability of fentanyl sublingual tablets (FST, Abstral), compared with placebo, for the treatment of BTP in opioid-tolerant patients with cancer. This was a randomized, placebo-controlled, multicenter, multiple-dose phase 3 trial with 36 participating clinical centers in the U.S.

Methods¹⁷

Eligible patients included those who were 17 years of age or older with stable cancer-related pain, regularly experiencing one to four episodes of BTP per day while receiving fixed-schedule oral opioid treatment equivalent to oral morphine 60 to 1,000 mg/day or transdermal fentanyl 50 to 300 mcg/hour, and an Eastern Cooperative Oncology Group (ECOG) performance status score ranging between 0 and 2. Exclusion criteria included (1) uncontrolled or rapidly escalating pain, (2) clinically significant conditions that would prevent study participation or increase risks of treatment with potent opioids, based on the investigators' opinions, and (3) treatment with monoamine oxidase (MAO) inhibitors within 14 days or strontium 89 60 days prior to study randomization and enrollment. Patients were allowed to continue adjunctive therapy for pain (e.g., physical therapy or acupuncture) if the regimen remained unchanged during study participation. Rescue medication was allowed as needed, with use recorded in patient diaries.

The study design included an open-label titration period, a two-week double-blind efficacy phase, and an open-label, long-term safety phase up to 12 months (Figure 5). Patients provided informed consent and were assessed for study eligibility at the screening visit. Eligible patients were instructed about the proper adminis-

TABLE 4
Summary of Adverse Events by Severity

| Adverse Event | Severity | | |
|-------------------------------|----------|----------|--------|
| | Mild | Moderate | Severe |
| Anemia | 1 | 0 | 0 |
| Dizziness* | 1 | 0 | 0 |
| Fever | 0 | 0 | 1 |
| Hematuria | 1 | 0 | 0 |
| Increase in pain | 0 | 1 | 0 |
| Intense lower abdominal pain† | 0 | 0 | 1 |
| Nausea/vomiting* | 0 | 1 | 0 |
| Sensation of swollen face | 2 | 0 | 0 |
| Urinary retention | 0 | 0 | 1 |
| Urinary tract infection | 1 | 0 | 0 |
| Vomiting and pain | 0 | 0 | 1 |

* Treatment-related.
† Serious adverse event.
Progression of cancer and septicemia are each reported for one patient with severity not specified but are classified as serious adverse events.
From Lennernäs B, Frank-Lissbrant I, Lennernäs H, et al. *Palliat Med* 2010;24(3):286–293.²⁷

tration of FST, followed by a two-week, open-label titration phase with a starting dose of FST 100 mcg. Inadequate pain relief in response to the 100-mcg dose prompted treatment with rescue medication, and the next higher dose of FST was administered at the next occurrence of BTP. The occurrence of intolerable AEs following the 100-mcg dose prompted study discontinuation, while AEs associated with doses greater than 100 mcg prompted reduction of the dose of FST at the next episode of BTP. Doses of FST were titrated upward to a maximum of 800 mcg until patients identified a dose that provided effective pain relief for all BTP occurrences for two consecutive days with at least one BTP episode on each of the two days. FST was evaluated at doses of 100, 200, 300, 400, 600, and 800 mcg.

Following successful dose titration, eligible patients completed a two-week, double-blind efficacy evaluation phase. During this period, patients received 10 doses of the study medication, including seven doses of FST at the patient-identified effective dose and three doses of matching placebo. Each of the 10 episodes of BTP was separated by a minimum of two hours. Patients received one dose of the study medication in random order, with placebo doses separated by at least a single dose of the

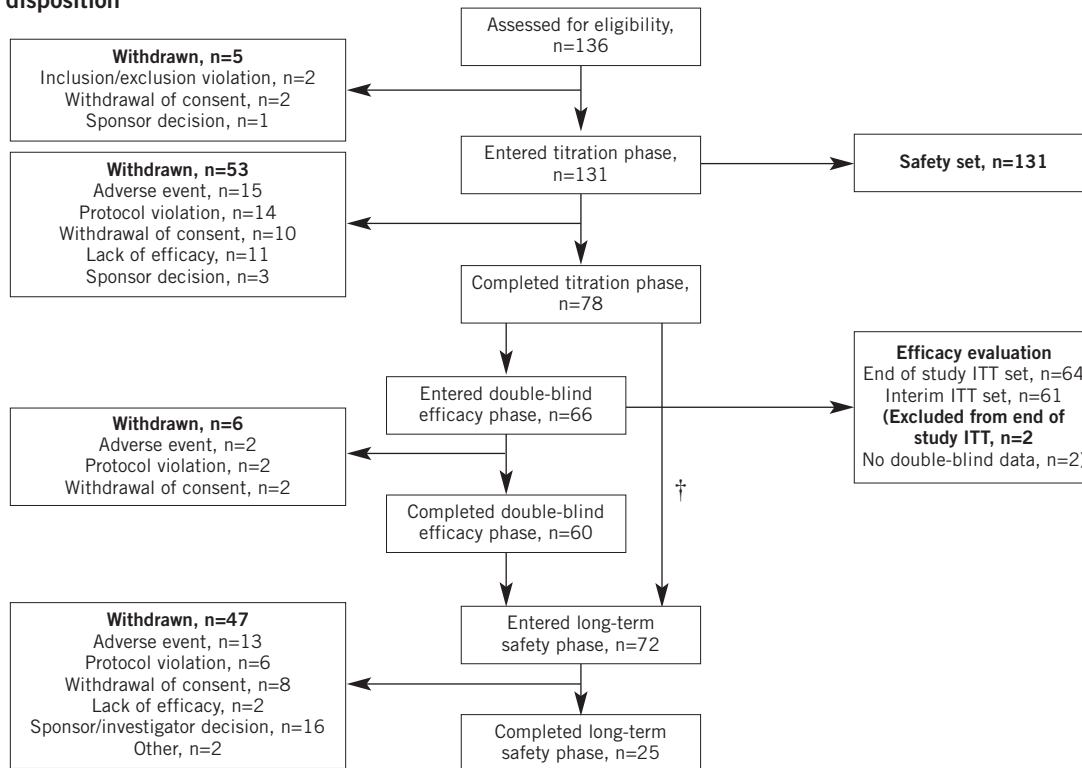
study medication. Rescue medication was administered to patients who experienced an occurrence of BTP within two hours of previous receipt of the study drug. During both the titration and efficacy phases, at least two hours elapsed between administration of the study medication. Telephone follow-up was conducted daily with patients to monitor their use of FST, rescue medications, and the type and frequency of AEs.

Following completion of the efficacy phase, patients were eligible to enter an open-label, long-term safety phase during which FST was administered as needed to treat BTP occurrences for up to 12 months. During the safety phase, in-person follow-up meetings with each patient were conducted monthly. Telephone follow-up was conducted two weeks following each monthly site visit.

Study Assessments: Efficacy and Safety¹⁷

All efficacy assessments were recorded by patients in an electronic diary. The primary study endpoint was the sum of pain intensity difference (SPID) from baseline to 30 minutes following treatment with the study drug for each episode of BTP. Secondary efficacy endpoints included:

FIGURE 5
Patient disposition



ITT = intent to treat.

† Patients who completed the titration phase after the interim analysis entered directly into the long-term safety phase.

From Rauck R, Tark M, Reyes E, et al. *Curr Med Res Opin* 2009;25(12):2877-2885.¹⁷

- SPID over 60 minutes, calculated under the curve of PID against time.
- pain intensity rated on 11-point scale ranging from 0 (no pain) to 10 (worst pain imaginable).
- pain intensity assessed immediately before administration of each dose of the study drug and at 10, 15, 30, and 60 minutes afterward.
- PID score calculated by subtracting pain ratings at each time point from the pain intensity rating at baseline.
- pain relief reported by patients at 10, 15, 30, and 60 minutes following treatment with the study drug for each event of BTP measured on a 5-point scale ranging from 0 (no relief) to 4 (complete relief).
- patient satisfaction with the medication measured by the Patient Global Evaluation of Medication (PGEM) scale assessed at screening, 60 minutes following administration of each dose of study drug during the efficacy phase, following the use of rescue medication, and during the long-term safety phase with satisfaction ratings recorded on 5-point scale ranging from 1 (excellent) to 5 (poor).
- the percentage of responders defined as patients achieving a decrease of 30% or more in pain intensity, compared with baseline at 30 minutes, following treatment with the study drug.
- the use of rescue medications.

AEs were recorded by investigators during study visits and telephone follow-up. An AE was defined as any unfavorable or unintended change in signs, symptoms, or laboratory results or exacerbation of a pre-existing condition. All AEs were evaluated for severity, duration, and their relationship with the study drug. Assessments of oral mucositis were based on examination of the oral mucosa for erythema and ulcers at each clinic visit for the duration of the trial.

The statistical analysis plan included a prespecified interim analysis based on 75% of the total planned patient enrollment with early study cessation if there was evidence that FST demonstrated overwhelming efficacy ($P \leq 0.0414$). The ITT population included all randomly assigned patients who received at least one dose of the study medication during the double-blind efficacy phase and provided a pain-intensity score at baseline and at least one evaluation of pain intensity during the efficacy phase.

The primary analysis of efficacy included the ITT population at the interim analysis (the interim ITT set), and the secondary efficacy analyses included the full ITT population. Safety and tolerability analyses included all patients who entered the titration phase (the safety set). Analysis of variance (ANOVA) compared SPID, PID, and pain relief between treatment groups while the comparison of PGEM scores between groups was evaluated with analysis of covariance (ANCOVA).

The last observation carried forward (LOCF) was used to impute missing data for BTP episodes requiring rescue medications, study discontinuation for reasons other than AEs, and baseline observation carried forward (BOCF) for study discontinuations caused by AEs.

Results¹⁷

Of 136 patients screened for study eligibility, 131 entered the titration phase and 78 (59.5%) completed this phase. A total of 66 patients entered the double-blind efficacy phase with 60 of these extending their participation to the long-term safety study; 12 patients enrolled in the long-term safety phase immediately. A review of baseline demographic and clinical characteristics established that mean age of study participants was 55 years; 54.2% were women and 84% were Caucasian (Table 5). The baseline demographic characteristics were similar between patients completing the titration phase, those who withdrew during titration, and patients who enrolled in the long-term safety phase.

Efficacy results. The primary efficacy analysis of the interim ITT population ($n = 61$) included 393 BTP episodes treated with FST and 168 treated with placebo. The mean SPID at 30 minutes post-dose was significantly greater for FST (49.5) compared with placebo (36.6; $P = 0.0004$) (Figure 6). Significant improvements were evident for SPID among patients treated with FST (143.0) compared with placebo (104.5; $P = 0.0002$). In addition, significantly better PID scores were evident from 10 minutes after administration of FST compared with placebo ($P = 0.0055$) and were sustained for 60 minutes ($P \leq 0.0055$).

Significantly greater pain relief was associated with FST from 10 minutes through 60 minutes compared with placebo ($P \leq 0.049$) (Figures 7 and 8). The mean PGEM for FST was 3.1, compared with 3.6 for placebo ($P = 0.0006$). At the study's completion, 29.7% of patients were very satisfied and 17.2% were satisfied with FST. The percentage of responders to FST was 86.9%, compared with 64.9% of those who had been treated with placebo. The use of rescue medications was lower for BTP episodes treated with FST (11.2) compared with 27.4% of episodes treated with placebo.

Analysis of the end-of-study ITT population ($n = 64$) confirmed the primary analysis with significantly better SPID for FST at 30 and 60 minutes compared with placebo ($P \leq 0.0004$). Mean PID and pain relief scores were also significantly higher for patients treated with FST compared with placebo at 10, 15, 30, and 60 minutes following administration of each dose ($P \leq 0.0054$ for mean PID and ≤ 0.027 for pain relief comparing FST with placebo).

Safety results. The median duration of treatment with FST was 51 days with median duration of treatment of eight days for the titration phase, six days for the efficacy phase, and 161.5 days for the long-term safety component

TABLE 5
Baseline Characteristics of the Study Population

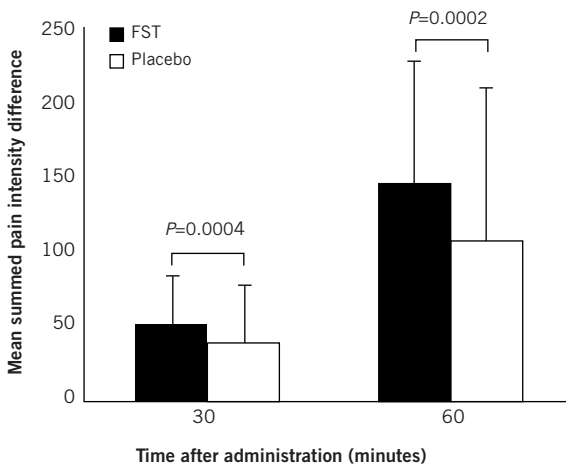
| Characteristic | Total No. of Patients Treated (N = 131) | Patients Who Completed Titration Phase and Entered Efficacy Phase (n = 66) | Patients Who Withdrew During Titration Phase (n = 53) | Patients Who Entered Long-Term Safety Phase (n = 72) |
|----------------|---|--|---|--|
| Age, years | | | | |
| • Mean (SD) | 55.0 (11.5) | 53.3 (11.3) | 56.2 (11.4) | 53.6 (11.7) |
| • Range | 21–80 | 21–80 | 22–80 | 21–80 |
| Sex, n (%) | | | | |
| • Female | 71 (54.2) | 35 (53.0) | 29 (54.7) | 39 (54.2) |
| • Male | 60 (45.8) | 31 (47.0) | 24 (45.3) | 33 (45.8) |
| Race, n (%) | | | | |
| • Asian | 3 (2.3) | 2 (3.0) | 1 (1.9) | 2 (2.8) |
| • Black | 6 (4.6) | 1 (1.5) | 4 (7.5) | 2 (2.8) |
| • White | 110 (84.0) | 56 (84.8) | 43 (83.1) | 61 (84.7) |
| • Other | 12 (9.2) | 7 (10.6) | 5 (9.4) | 7 (9.7) |

From Rauck R, Tark M, Reyes E, et al. *Curr Med Res Opin* 2009;25(12):2877–2885.¹⁷

of the trial. Fifty-two patients received three or more months of treatment with FST, for a total of 38,015 episodes of BTP treated during the long-term safety phase (Table 6). The median dose of FST during the long-term safety phase was 600 mcg (range, 100–800 mcg; mean, 550.8 mcg).

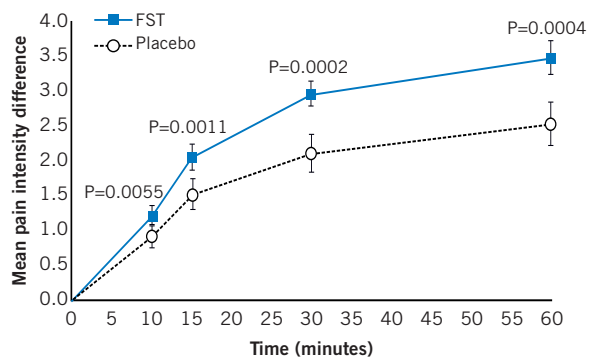
The median number of doses of FST taken during the long-term safety phase was three doses per day (mean, 2.9 doses; range, one to six doses). One or more treatment-related AEs were reported by 96 of 131 patients (73.3%), and 33 of 96 (25.2%) of these patients experiencing at least one AE that was considered severe (Table 7). Treatment-related adverse reactions considered related to the

FIGURE 6
Mean pain intensity differences between fentanyl sublingual tablets (FST) and placebo by time after administration



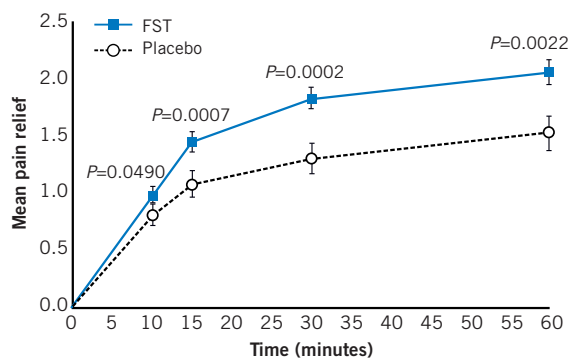
Error bars represent standard deviation. Adapted from Rauck R, Tark M, Reyes E, et al. *Curr Med Res Opin* 2009;25(12):2877–2885.¹⁷

FIGURE 7
Mean pain intensity difference over time



Error bars represent standard deviation. Adapted from Rauck R, Tark M, Reyes E, et al. *Curr Med Res Opin* 2009;25(12):2877–2885.¹⁷

FIGURE 8
Mean pain relief over time



Error bars represent standard deviation. Adapted from Rauck R, Tark M, Reyes E, et al. *Curr Med Res Opin* 2009;25(12):2877–2885.¹⁷

study medication were experienced by 41 of 131 patients (31.3%).

The most frequently reported drug reactions were nausea (12.2%), vomiting (5.3%), and somnolence (4.6%). The incidence of oral mucositis was low, with only one patient experiencing stomatitis considered possibly or probably related to FST. Thirty patients discontinued study participation as a result of treatment-emergent AEs, including GI disorders (4.6%), neoplasms (4.6%), and psychiatric disorders (3.8%); 17 of the 30 treatment-emergent AEs were considered probably or possibly related to the study medication, including dyspnea, nausea, and vomiting (n = 2 for each event). Serious AEs were reported for 18.3% of patients (n = 24), although only one serious AE (mild affect lability) was considered possibly associated with the study drug. A total of 10 deaths occurred, although none of the deaths was attributed to the study drug.

Nonrandomized Phase 3 Study of the Long-Term Effectiveness and Safety of Sublingual Fentanyl For Cancer Patients with Breakthrough Pain

Overview of Trial Design and Objectives²⁸

A phase 3, U.S.-based multicenter, multiple-dose, non-randomized, open-label study was conducted by Nalachu et al. to evaluate the long-term effectiveness and safety of fentanyl sublingual tablets (FST) in opioid-tolerant patients with breakthrough cancer pain.

Methods²⁸

The study comprised a two-week open-label titration phase, followed by a long-term maintenance phase of up to 12 months.

Opioid-tolerant male and female patients 17 years of age and older with stable cancer-related pain were recruited. Patients regularly experienced one to four episodes of breakthrough cancer pain per day while receiving stable, fixed-schedule pain medication equivalent to 60 to 1,000 mg of oral morphine per day or transdermal fentanyl therapy equivalent to 50–300 mcg/hour.

Exclusion criteria included previous exposure to sublingual fentanyl orally disintegrating tablets, uncontrolled or rapidly escalating pain; any clinical condition that could preclude participation or compromise data collection; antineoplastic therapy that would influence the assessment of breakthrough pain; receipt of monoamine oxidase inhibitors during the study; and allergy or contraindications to fentanyl.

Patients received FST in an open-label fashion to treat episodes of pain as required. During the two-week open-label titration phase, the dosage of FST was titrated upward from 100 mcg to a maximum of 800 mcg until a stable dose was identified that successfully treated all episodes of breakthrough pain for two consecutive days.

Patients continued to receive FST at the identified

TABLE 6
Summary of Overall Treatment Characteristics For the Long-Term Safety Phase

| Treatment Variable | Long-Term Safety Phase (n=72) |
|--|-------------------------------|
| Treatment duration, median (days) | 161.5 |
| Total episodes of BTP treated with FST | 38,015 |
| FST dose, mcg <ul style="list-style-type: none"> • Median • Mean • Range | 600 550.8 100–800 |
| FST doses/day <ul style="list-style-type: none"> • Median • Mean • Range | 3 2.9 1–6 |
| BTP = breakthrough pain. From Rauck R, Tark M, Reyes E, et al. <i>Curr Med Res Opin</i> 2009; 25(12):2877–2885. ¹⁷ | |

TABLE 7
Summary of Treatment-Emergent* Adverse Events Experienced by at Least 2% of Patients

| Adverse Reactions | Safety Population (N = 131) |
|--|-----------------------------------|
| Gastrointestinal, n (%) <ul style="list-style-type: none"> • Nausea • Vomiting | 22 (16.8) 16 (12.2) 7 (5.3) |
| Nervous system disorders, n (%) <ul style="list-style-type: none"> • Headache • Somnolence | 15 (11.5) 5 (3.8) 6 (4.6) |
| *Treatment-emergent adverse events were considered possibly or probably related to the study medication. From Rauck R, Tark M, Reyes E, et al. <i>Curr Med Res Opin</i> 2009; 25(12):2877–2885. ¹⁷ | |

stable dose throughout the long-term safety phase as required. Consecutive doses were separated by two hours or more.

Fixed-schedule opioid medications were to remain unchanged during the titration phase, but they could be changed during the long-term safety phase if clinically indicated. Rescue medication was permitted, if required, 30 minutes or more after FST was administered.

Study Assessments: Efficacy and Safety²⁸

The effectiveness of FST was assessed based on the Patient Global Evaluation of Medication. Patients rated their overall satisfaction with their pain medication on entry to the study and with FST compared with their previous pain medication, as “very satisfied,” “satisfied,” “no preference,” “dissatisfied,” “very dissatisfied.” Satisfaction was assessed at each monthly site visit.

Effectiveness was also evaluated using the Brief Pain Inventory (BPI), which comprised six questions relating to seven aspects of daily functioning. Patients rated their

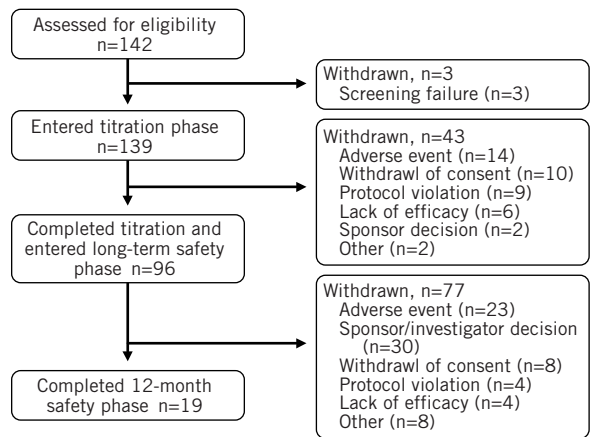
worst, least, and average pain in the previous 24 hours and pain at the time of assessment using a numerical scale from 0 (“no pain”) to 10 (“pain as bad as you can imagine”).

Changes in psychological factors associated with pain were recorded using the Depression, Anxiety, and Positive Outlook Scale (DAPOS), comprising 11 statements among three quality-of-life domains (depression, anxiety, and well-being). Patients indicated their agreement with the statements on a 5-point scale ranging from 1 (“almost never”) to 5 (“almost all the time”). Higher scores correspond to greater depression, greater anxiety, and greater well-being. Adverse events (AEs) were recorded throughout the study, at each study visit, and in telephone follow-ups.

Results²⁸

A total of 142 patients were screened, of whom 139 entered the titration phase and 96 patients identified an effective stable dose of FST (Table 8 and Figure 9). Forty-three patients withdrew during the titration phase. The most common reasons for withdrawal included AEs (in 14 patients) and withdrawal of consent (in 10 patients) (see Figure 9). Only 10 patients withdrew because of a

FIGURE 9
Summary of patient disposition in a phase 3 study



From Nalamachu S, Hassman D, Wallace MS, et al. *Curr Med Res Opin* 2011;27(3):519–530 (in press). © 2011, Informa Healthcare.²⁸

lack of treatment efficacy (six patients withdrew during the titration phase, and four patients withdrew during the long-term safety phase).

Nineteen patients completed the full 12-month safety phase (see Figure 9).

Of the patients who discontinued during the long-term safety phase, 24 patients were withdrawn as a result of the sponsor’s decision (i.e., because of overall favorable program results).

Efficacy results. The Patient Global Evaluation of Medication indicated that a higher proportion of patients were “satisfied” or “very satisfied” with FST at the end of study assessment, compared with treatment given before the study. Of those patients who completed effectiveness evaluations, 71 of 92 subjects (77%) reported being satisfied or very satisfied with their pain medication at the end of the study, compared with 70 of 130 patients (54%) at screening.

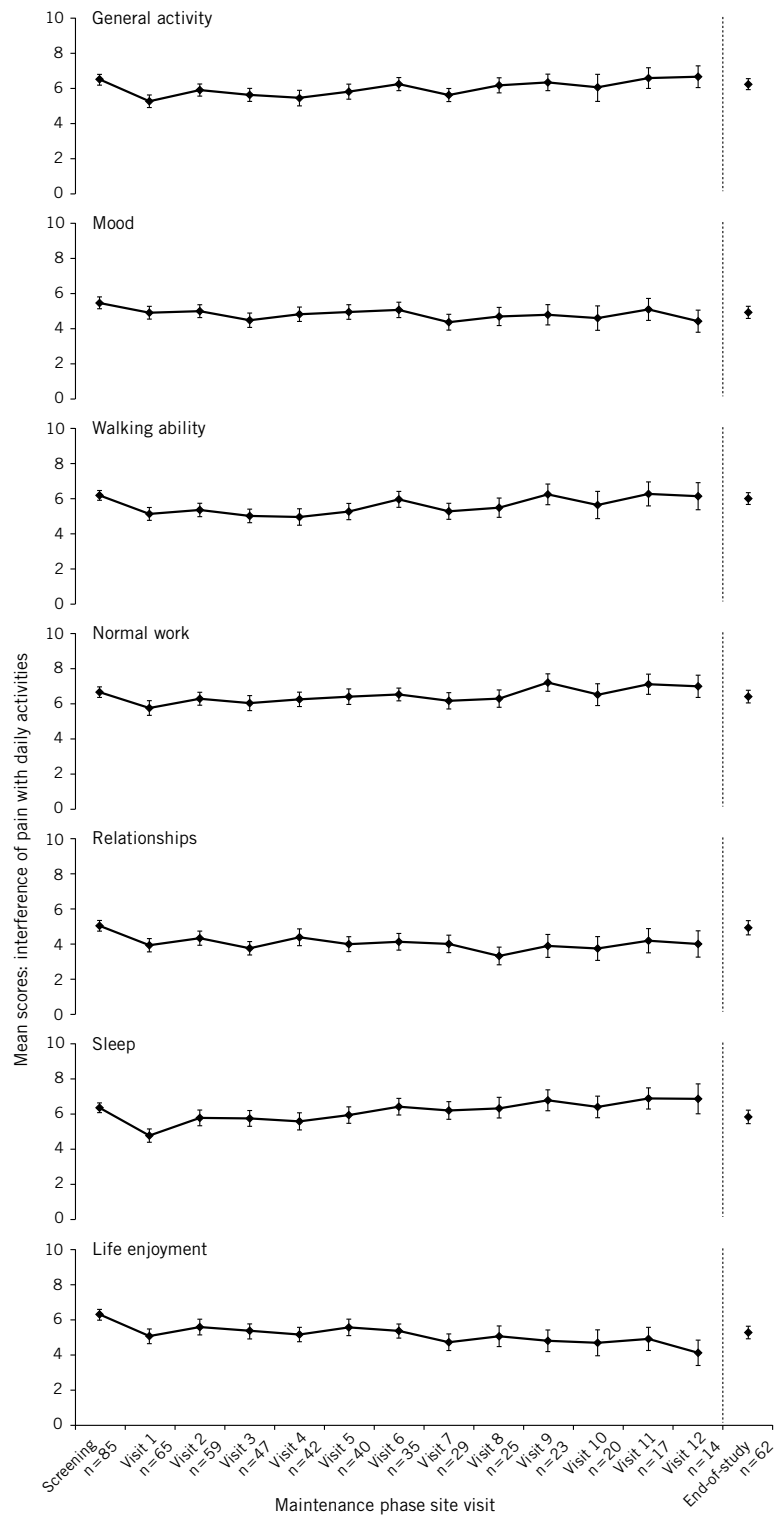
The investigators assessed quality of life in 85 patients by analyzing their responses on the BPI and DAPOS questionnaires. The BPI evaluation indicated that mean levels of pain severity generally remained stable throughout the study, except for current pain, which was significantly lower at the six-month visit, compared with screening ($P = 0.01$). By contrast, mean BPI scores showed statistically significant improvement in pain relief at both the six-month and end-of-study visits, compared with screening at baseline ($P < 0.05$). BPI scores also indicated less interference with daily functioning, suggesting improvements at the end of the study, as indicated by lower scores. The composite score for interference of pain with daily functioning was improved at six months and at the end of the study, and statistically significant reductions were recorded at six months ($P < 0.001$). Mean scores for

TABLE 8
Baseline Demographics and Characteristics

| | Entered Study (n=139) | Discontinued During Titration Phase (n=43) | Completed Titration and Entered Long-Term Safety Phase (n=96) |
|--------------------------------|-----------------------|--|---|
| Age (years) | | | |
| Mean (SD) | 57 (11.6) | 58.3 (12.0) | 56.4 (11.5) |
| Range | 28–85 | 31–82 | 28–85 |
| Race, n (%) | | | |
| White | 116 (83.5) | 32 (74.4) | 84 (87.5) |
| Black/African American | 11 (7.9) | 5 (11.6) | 6 (6.3) |
| Asian | 1 (0.7) | 1 (2.3) | 0 |
| American Indian/Alaskan Native | 1 (0.7) | 1 (2.3) | 0 |
| Hispanic or Latino | 10 (7.2) | 4 (9.3) | 6 (6.3) |
| Sex, n (%) | | | |
| Female | 76 (54.7) | 20 (46.5) | 56 (58.3) |
| Male | 63 (45.3) | 23 (53.5) | 40 (41.7) |

From Nalamachu S, Hassman D, Wallace MS, et al. *Curr Med Res Opin* 2011;27(3):519–530 (in press). © 2011, Informa Healthcare.²⁸

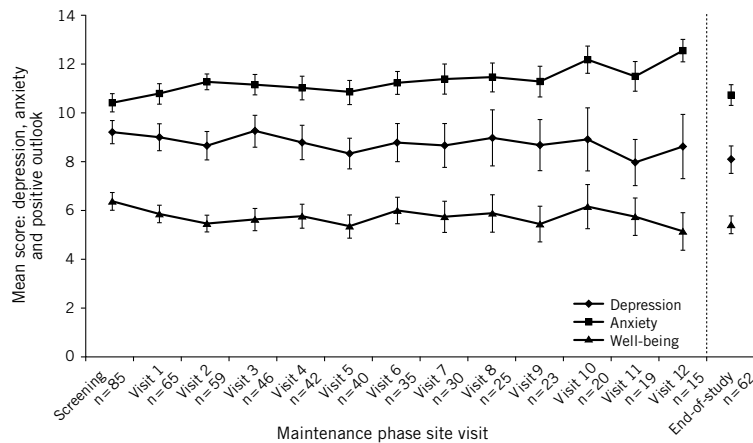
FIGURE 10
Mean Brief Pain Inventory (BPI) scores for seven assessed aspects of interference with daily activities



Error bars represent standard error.

From Nalamachu S, Hassman D, Wallace MS, et al. *Curr Med Res Opin* 2011;27(3):519-530 (in press). © 2011, Informa Healthcare.²⁸

FIGURE 11
Mean scores for the three domains of the Depression, Anxiety, and Positive Outlook Scale (DAPOS)



Error bars represent standard error.
 From Nalamachu S, Hassman D, Wallace MS, et al. *Curr Med Res Opin* 2011;27(3):519–530 (in press). © 2011, Informa Healthcare.²⁸

TABLE 9
Summary of Study Drug-Related Adverse Events Experienced by at Least 2% of Patients

| | n (%) |
|---|------------------|
| Total No. of study drug-related adverse events | 49 (35.3) |
| Gastrointestinal disorders | 27 (19.4) |
| Nausea | 12 (8.6) |
| Vomiting | 3 (2.2) |
| Dry mouth | 5 (3.6) |
| Constipation | 8 (5.8) |
| General disorders and administration-site conditions | 6 (4.3) |
| Fatigue | 6 (4.3) |
| Nervous system disorders | 21 (15.1) |
| Dizziness | 4 (2.9) |
| Headache | 5 (3.6) |
| Somnolence | 8 (5.8) |

From Nalamachu S, Hassman D, Wallace MS, et al. *Curr Med Res Opin* 2011;27(3):519–530 (in press). © 2011, Informa Healthcare.²⁸

each of the seven aspects of daily functioning are shown in Figure 10.

DAPOS scores showed numerical trends toward improvements in all three quality-of-life domains at the end of the study when compared with screening (Figure 11). Depression scores were also statistically significantly improved at six months ($P = 0.011$).

Safety results. All 139 patients received at least one dose of study medication, and 62 patients received FST for more than three months. The median duration of exposure to FST during the long-term safety phase was 149 days. The mean stable dose identified during the titration phase was 475 mcg (median, 400 mcg).

For the 96 patients who entered the long-term safety phase, a total of 46,952 episodes of breakthrough cancer pain were treated with FST. Overall, 116 of 139 patients (83.5%) experienced at least one AE, and 49 of 139 patients (35.3%) experienced AEs that were considered possibly or probably related to the study drug.

The most commonly reported AEs included nausea (23%), fatigue (15.1%), and vomiting (12.9%). The most common study drug-related AEs included nausea (8.6%), constipation (5.8%), and somnolence (5.8%) (Table 9). Most AEs (44.6%) were considered mild or moderate in severity, compared with 38.8% of those considered to be severe AEs.

Thirty-seven patients withdrew from the study as a result of AEs (14 patients during the titration phase and 23 patients during the long-term safety phase).

Overall, serious AEs were reported by 46 of 139 patients (33.1%), and 19 patients died during the study. None of the serious AEs or deaths were considered possibly or probably related to FST; these deaths were primarily related to cancer progression or complications from the disease or disease treatment.

P&T Committee Considerations

DRUG DELIVERY SYSTEM

A rapid onset of pharmacological effect is often desirable when treating acute disorders and severe pain. Quick relief can be achieved with parenteral administration, but this method is not always convenient for the patient. Therefore, there is growing interest in developing new, non-parenteral, reliable and convenient dosage forms using administration routes in which a rapidly dissolved drug is immediately absorbed into the systemic circulation.²²

Oromucosal delivery is a promising drug delivery route that promotes rapid absorption and high bioavailability, with onset of pharmacological effect within 10 minutes in the case of fentanyl sublingual tablets (FST, or Abstral). As a result of the drug directly entering the systemic circulation, bypassing the gastrointestinal tract and the first pass effect in the liver, tablet formulations used for oromucosal delivery allow for a short disintegration and dissolution time.²²

Many oromucosal delivery systems, however, are compromised by the possibility of the patient swallowing the active substance before it has been released and absorbed locally into the systemic circulation. To increase retention of fentanyl citrate at the site of absorption in the oral cavity, a bioadhesive component was added to the carrier particles of FST.²²

FST containing 100, 200, and 400 mcg of fentanyl citrate, along with the bioadhesive component (polyvinylpyrrolidone) was tested *in vitro*, with the result that the fentanyl citrate disintegrated in 33 to 50 seconds when discs were used and in less than 10 seconds without discs. To date, this has not been proven to correlate with *in vivo* data. Plasma concentrations of fentanyl were obtained within 10 minutes, with no second peak. There is a mucoadhesive component to the formulation, and the micronized mannitol carrier particles are designed to increase the area available for drug absorption.²²

In vitro data show a rapid disintegration time with FST. Fentanyl buccal tablets (Fentora) must be left in place for 14 to 25 minutes until the tablet is dissolved,¹⁸ and the fentanyl citrate oral transmucosal lozenge (Actiq) requires the patient to move the drug around in the mouth and twirl the handle often, for a period of 15 minutes.¹⁹ Approximately 25% of the total dose of Actiq is rapidly absorbed from the buccal mucosa and becomes systemically available; the remaining 75% of the total dose is swallowed with the saliva and then is slowly absorbed from the gastrointestinal (GI) tract.¹⁹ Similarly with fentanyl buccal tablets, approximately 50% of the total dose is absorbed transmucosally and becomes systemically available; the remaining half of the dose is swallowed and undergoes more prolonged absorption from the GI tract.¹⁸

EFFICACY

The efficacy and safety of FST for the treatment of breakthrough pain (BTP) in opioid-tolerant patients was established in three recent clinical trials. The first was a phase 2 study that demonstrated effective analgesic effects of FST for the treatment of BTP in opioid-tolerant patients with cancer with significant differences evident for all three doses compared with placebo; the greatest relief was associated with the FST 400-mcg dose.²⁷

Significant improvements in pain intensity difference (PID) were evident 15 minutes following treatment with the 400-mcg dose ($P = 0.02$).²⁷ Improvements in pain control were evident as soon as 5 minutes following administration of FST, although this trend did not become statistically significant until the 15-minute assessment of PID.²⁷ These results confirm the rapid absorption and fast onset of action of FST, which are considered essential elements for the optimal treatment of BTP.^{5-7,20}

The increased pain relief achieved by FST was associated with significant reductions in the use of rescue medications and improvements in patients' global assessments of treatment for those receiving FST 400 mcg.²⁷ The AE profile for FST was comparable to other opioids, with nausea, vomiting, and dizziness reported to be the most common side effects. There was no evidence to suggest that the AEs associated with FST differed from those associated with other transmucosal fentanyl products.²⁷

Results from the first large-scale phase 3 trial to evaluate the efficacy and safety of FST across all approved dose ranges for treatment of BTP episodes in opioid-tolerant cancer patients support earlier phase 1 and 2 studies that showed rapid onset of the analgesic effects of FST.¹⁷ Evaluation of the primary endpoint revealed significantly greater improvements in sum of pain intensity difference (SPID) at 30 minutes compared with placebo. The onset of pain relief was significantly faster for FST compared with placebo with significant differences evident at 10 minutes after administration.¹⁷ Furthermore, relief of BTP was sustained for 60 minutes, which was significantly better compared with placebo.¹⁷ Ratings of PID and pain relief were also significantly better for FST compared with placebo at all time point assessments for up to 60 minutes.¹⁷

Patients treated with FST required significantly less rescue medication, reported greater satisfaction with pain relief, and had a higher rate of pain response compared with placebo.¹⁷ These results establish that FST offers effective, rapid relief of BTP episodes with analgesic effects evident for doses ranging from 100 to 800 mcg.¹⁷ Safety assessments confirm that FST was systemically

and sublingually well tolerated when used over the long term.¹⁷

The most commonly reported AEs were nausea, vomiting, and somnolence, which are frequently associated with all opioid analgesic agents.¹⁷ The provision of patient choice of dose allowed achievement of the optimal balance between effective pain relief and an acceptable side effect profile with 59.5% of patients identifying a stable dose of FST to treat BTP with an effective dose identified within the first two weeks of treatment by most patients.¹⁷

Another recent phase 3, open-label, multicenter study was conducted in opioid-tolerant patients 17 years of age or older with breakthrough cancer pain. The study comprised a two-week titration phase. This was followed by a maintenance phase of up to 12 months in which patients self-administered FST for episodes of breakthrough cancer pain. Patients' Global Evaluation of Medication (PGEM), the BPI, and the DAPOS were used to measure the drug's effectiveness.²⁸

Of 139 recruited patients, 69% identified an effective dose of FST (a dosage that successfully treated all episodes of breakthrough cancer pain over two consecutive days). They then entered the maintenance phase, during which they were treated for a median of 149 days with a mean dose of 507.5 mcg.

The study recorded a significant increase in reported satisfaction with pain medication at the six-month and end-of-study visits, compared with screening ($P \leq 0.01$). The DAPOS and BPI identified no deterioration in scores and showed significant improvements in patient satisfaction and quality of life ($P < 0.05$).

FST was well tolerated, with no study drug-related deaths; 49 patients (35.3%) experienced one or more treatment-related AEs. The most common AEs included nausea (8.6%), constipation (5.8%), and somnolence (5.8%). There was no evidence of sublingual mucosal irritation caused by the study medication. The pattern of AEs was similar to that previously observed with transmucosal fentanyl, and there was an acceptable safety profile over 12 months of treatment.²⁸

SAFETY²⁶

Contraindications

FST is contraindicated in the management of pain in opioid-non-tolerant patients, because life-threatening hypoventilation can occur at any dose in patients not already taking around-the-clock opioid therapy. Patients considered opioid-tolerant are those who are taking at least 60 mg of morphine/day or at least 25 mcg of transdermal fentanyl/hour, 30 mg of oral oxycodone/day, 8 mg of oral hydromorphone/day, 25 mg of oral oxycodone/day, or an equianalgesic dose of another opioid for a week or longer.

FST is contraindicated in the management of acute or postoperative pain, including headache or migraine, dental pain, or use in the emergency room. It is also con-

traindicated in patients with known intolerance or hypersensitivity to any of its components or the drug fentanyl. Anaphylaxis and hypersensitivity have been reported in association with the use of other oral transmucosal fentanyl products.

FST and Other Fentanyl Products. FST is *not* equivalent to all other fentanyl products used to treat breakthrough pain on a mcg-per-mcg basis. There are differences in the pharmacokinetics of FST relative to other fentanyl products that could potentially result in clinically important differences in the amount of fentanyl absorbed and could result in a fatal overdose.

When prescribing FST to a patient, *do not* convert from other fentanyl products without retitrating according to the instructions found in the prescribing information. When dispensing FST, *do not* substitute it for any other fentanyl product prescription.

Directions for safely converting patients to FST from other fentanyl products are not currently available. (*Note:* This includes oral, transdermal, or parenteral formulations of fentanyl.) Therefore, for opioid-tolerant patients starting treatment for breakthrough pain, the initial dose of FST is 100 mcg. Individually titrate each patient's dose to provide adequate analgesia while minimizing side effects.

Respiratory Depression. Serious or fatal respiratory depression can occur even at recommended doses in patients using FST. Respiratory depression is more likely to occur in patients with underlying respiratory disorders and elderly or debilitated patients, usually following large initial doses, including FST, in opioid non-tolerant patients, or when opioids are given in conjunction with other drugs that depress respiration.

Respiratory depression from opioids is manifested by a reduced urge to breathe and a decreased rate of respiration, often associated with the "sighing" pattern of breathing (deep breaths separated by abnormally long pauses). Carbon dioxide retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. This makes overdoses involving drugs with sedative properties and opioids especially dangerous.

Instructions for Patients and Caregivers. *Patients and their caregivers must be instructed that FST contains a medication in an amount that can be fatal to a child.* Even though FST is provided in child-resistant packaging, patients and their caregivers must be instructed to keep tablets out of the reach of children.

Taking FST could be fatal in individuals for whom it is not prescribed and for those who are not opioid-tolerant.

Physicians and dispensing pharmacists must specifically question patients or caregivers about the presence of children in the home (on a full-time or visiting basis) and counsel them regarding the dangers to children from inadvertent exposure.

Additive CNS Depressant Effects. The concomitant

Warnings and Precautions²⁶**Boxed Warning: Potential for Abuse and Importance of Proper Patient Selection**

- **Abstral (FST) contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics.** FST can be abused in a manner similar to other opioid agonists, legal or illicit. Consider the potential for abuse when prescribing or dispensing FST in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.
- Serious adverse events, including deaths, in patients treated with other oral transmucosal fentanyl products have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of FST for any other fentanyl product may result in fatal overdose.
- **FST is indicated only for the management of breakthrough cancer pain in patients 18 years of age and older who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.** Patients considered opioid tolerant are those who are taking at least 60 mg of morphine/daily, or at least 25 mcg of transdermal fentanyl/hour, or at least 30 mg of oxycodone daily, or at least 8 mg of oral hydromorphone daily, at least 25 mg of oral oxymorphone daily or an equianalgesic dose of another opioid for a week or longer.
- **FST is contraindicated in opioid non-tolerant patients** and is contraindicated in the management of acute or postoperative pain, including headache/migraine, dental pain, or use in the emergency room. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with other fentanyl products.
- When prescribing, do not convert patients on a mcg per mcg basis from another fentanyl product to FST. Patients beginning treatment with FST must begin with titration from the 100-mcg dose.
- When dispensing, do not substitute an FST prescription for other fentanyl products. Differences exist in the pharmacokinetics of FST compared to other fentanyl products that could result in clinically important differences in the amount of fentanyl absorbed and could result in fatal overdose.
- Special care must be used when dosing FST. If the breakthrough pain episode is not relieved, patients must wait at least 2 hours before treating another episode of breakthrough pain with FST.
- FST is intended to be used only in the care of opioid tolerant cancer patients and only by health care professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.
- **Patients and their caregivers must be instructed that FST contains a medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant. All packs must be kept out of the reach of children.**
- The concomitant use of FST with cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations and may cause potentially fatal respiratory depression.
- **Because of the risk for misuse, abuse, and overdose, FST is available only through a restricted distribution program, required by the Food and Drug Administration, called the Abstral REMS (Risk Evaluation and Mitigation Strategy).** Under the Abstral REMS, health care professionals who prescribe to outpatients, pharmacies, and distributors must enroll in the program to prescribe, receive, dispense, and distribute FST, respectively. Further information is available at www.abstralrems.com or by calling 1-888-227-8725.

use of FST with other CNS depressants, including other opioids, sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers, skeletal muscle relaxants, sedating antihistamines, and alcoholic beverages, may produce increased depressant effects (e.g., hypoventilation, hypotension, and profound sedation).

Concomitant use with potent inhibitors of cytochrome P450 3A4 isoform (e.g., erythromycin, ketoconazole, and certain protease inhibitors) may increase fentanyl levels, resulting in increased depressant effects. Patients taking concomitant CNS depressants must be monitored for a change in opioid effects and the dose of FST adjusted, if warranted.

Effects on Ability to Drive and Use Machines. Opioid analgesics impair the mental and/or physical ability required for the performance of potentially dangerous tasks (e.g., driving a car or operating machinery). Patients taking FST should be warned of these dangers and counseled accordingly.

Chronic Pulmonary Disease. Because potent opioids can cause hypoventilation, FST should be titrated with caution in patients with chronic obstructive pulmonary disease or pre-existing medical conditions predisposing them to hypoventilation. In such patients, even normal therapeutic doses of FST may further decrease respiratory drive to the point of respiratory failure.

Head Injuries and Increased Intracranial Pressure. Administer FST with extreme caution in patients who may be particularly susceptible to the intracranial effects of CO₂ retention such as those with evidence of increased intracranial pressure or impaired consciousness. Opioids may obscure the clinical course of a patient with a head injury; use only if clinically warranted.

Cardiac Disease. Intravenous administration of fentanyl may produce bradycardia. Therefore, use FST with caution in patients with bradyarrhythmias.

Monamine oxidase (MAO) Inhibitors. FST is not recommended for use in patients who have received MAO inhibitors within the past 14 days. Severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics.

Drug Interactions

Fentanyl is metabolized mainly via the human cytochrome P450 3A4 isoenzyme system (CYP 3A4); therefore, potential interactions may occur when FST is given concurrently with agents that affect CYP 3A4 activity.

The concomitant use of FST with CYP 3A4 inhibitors (e.g., indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, telithromycin, aprepitant, diltiazem, erythromycin, fluconazole, grapefruit juice, verapamil, or cimetidine) may result in a potentially dangerous increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory

depression.

Patients receiving FST who begin therapy with, or increase the dose of, CYP 3A4 inhibitors need to be carefully monitored for signs of opioid toxicity over an extended period of time. The dosage should be increased conservatively.

The concomitant use of FST with CYP 3A4 inducers (e.g., barbiturates, carbamazepine, efavirenz, glucocorticoids, modafinil, nevirapine, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's wort, or troglitazone) may result in a decrease in fentanyl plasma concentrations, which could decrease the efficacy of FST. Patients receiving FST who stop therapy with, or decrease the dose of, CYP 3A4 inducers need to be monitored for signs of increased FST activity and the dose of FST must be adjusted accordingly.

Adverse Reactions

Because clinical trials are conducted under widely varying conditions, adverse event rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of FST has been evaluated in 311 opioid-tolerant cancer patients with breakthrough pain, and 270 of these patients were treated in multiple-dose studies. The duration of therapy for patients in multiple-dose studies ranged from 1 to 405 days, with an average duration of 131 days; 44 patients were treated for at least 12 months.

The most commonly observed adverse reactions with FST include typical opioid adverse reactions, such as nausea, constipation, somnolence and headache. Expect opioid side effects and manage them accordingly.

The clinical trials of FST were designed to evaluate safety and efficacy in treating patients with cancer and breakthrough pain; all patients were taking concomitant opioids, such as sustained-release morphine, sustained-release oxycodone or transdermal fentanyl, for their persistent pain.

The frequencies listed below represent adverse reactions that occurred in $\geq 1\%$ of patients from two clinical trials who experienced that reaction while receiving FST. Reactions are classified by system organ class:

- *Adverse reactions* (1% or more)
- *Cardiac disorders*: bradycardia, tachycardia.
- *Eye disorders*: vision blurred.
- *Gastrointestinal disorders*: abdominal pain, abdominal pain upper, aphthous stomatitis, constipation, dry mouth, dyspepsia, gingival ulceration, impaired gastric emptying, lip ulceration, mouth ulceration, nausea, stomach discomfort, stomatitis, tongue disorder, vomiting.
- *General disorders and administration site conditions*: asthenia, drug withdrawal syndrome, fatigue, malaise.

- *Immune system disorders:* drug hypersensitivity.
- *Injury, poisoning and procedural complications:* accidental overdose.
- *Metabolism and nutrition disorders:* anorexia, decreased appetite.
- *Nervous system disorders:* amnesia, disturbance in attention, dizziness, dysgeusia, headache, hypoesthesia, lethargy, parosmia, somnolence, tremor.
- *Psychiatric disorders:* affect lability, anxiety, confusional state, depression, disorientation, dysphoria, euphoric mood, insomnia, mental status changes, paranoia, sleep disorder.
- *Reproductive system and breast disorders:* erectile dysfunction.
- *Respiratory, thoracic and mediastinal disorder:* dyspnea, oropharyngeal pain, throat tightness.
- *Skin and subcutaneous disorders:* hyperhidrosis, night sweats, pruritus, rash, skin lesion.
- *Vascular disorders:* hypotension.

Overdosage

The manifestations of FST overdosage are expected to be similar in nature to intravenous fentanyl and other opioids, and are an extension of its pharmacological actions with the most serious significant effect being hypoventilation.

Immediate Management. Immediate management of opioid overdose includes removal of FST, if still in the mouth, ensuring a patent airway, physical and verbal stimulation of the patient, and assessment of level of consciousness, ventilatory and circulatory status.

Accidental Ingestion in the Opioid-Nontolerant Person. Provide ventilatory support, obtain intravenous access, and administer naloxone or other opioid antagonists as clinically indicated. The duration of respiratory depression following overdose may be longer than the effects of the opioid antagonist's action (e.g., the half-life of naloxone ranges from 30 to 81 minutes) and repeated administration may be necessary. Consult the package insert of the individual opioid antagonist for details.

Overdose in Opioid-Tolerant Patients. Provide ventilatory support and obtain intravenous access as clinically indicated. Judicious use of naloxone or another opioid antagonist may be warranted in some instances, but at the risk of precipitating an acute withdrawal syndrome.

General Considerations for Overdose. Management of severe FST overdose includes: securing a patent airway, assisting or controlling ventilation and establishing intravenous access. In the presence of hypoventilation or apnea, assist or control ventilation, and administer oxygen as indicated.

Carefully observe and appropriately manage patients with overdose until their clinical condition is well controlled.

Although muscle rigidity interfering with respiration has not been seen following the use of FST, this is possi-

ble with fentanyl and other opioids. If it occurs, manage it by using assisted or controlled ventilation, by an opioid antagonist, and as a final alternative, by a neuromuscular blocking agent.

INDICATIONS AND USAGE²⁶

FST is an opioid analgesic indicated only for the management of breakthrough pain in cancer patients, 18 years of age and older, who are already receiving, and who are tolerant to, opioid therapy for their underlying persistent cancer pain.

DOSAGE AND ADMINISTRATION²⁶

The objective of dose titration is to identify an optimal maintenance dose for ongoing treatment of breakthrough pain episodes. The optimal dose of FST will be determined by dose titration in individual patients.

The tablet should be administered on the floor of the mouth directly under the tongue and should be allowed to dissolve completely.

As with all opioids, the safety of patients using such products is dependent on health care professionals prescribing them in strict conformity with their approved labeling with respect to patient selection, dosing, and proper conditions for use. Only prescribers enrolled in the Abstral REMS program may prescribe FST.

Dose Titration

All patients must be carefully supervised until a dose that provides adequate analgesia with tolerable side effects is reached for breakthrough pain control.

Starting dose: FST should be individually titrated to a dose that provides adequate analgesia with tolerable side effects. For all patients, titration is begun with an initial dose of 100 mcg. As a result of differences in the pharmacokinetic properties and individual variability, even patients switching from other fentanyl-containing products to FST must start with the 100-mcg dose. FST is *not* a generic version of any other fentanyl product.

If adequate analgesia is obtained within 30 minutes of administration of the 100-mcg tablet, patients may continue to treat subsequent episodes of breakthrough pain with this dose.

If adequate analgesia is not obtained after FST is given, patients may use a second FST dose (after 30 minutes) as directed by their health care provider. No more than two doses of FST may be used to treat an episode of breakthrough pain.

Patients must wait at least two hours before treating another episode of breakthrough pain with FST. Consumption should be limited to treat four or fewer BTP episodes per day after a successful dose is established.

Titration steps: If adequate analgesia was not obtained with the first 100-mcg dose, dose escalation is continued in a stepwise manner over consecutive breakthrough episodes until adequate analgesia with tolerable

side effects is achieved. The dose is increased by 100-mcg multiples up to 400 mcg as needed.

If adequate analgesia is not obtained with a 400-mcg dose, the next titration step is 600 mcg. If adequate analgesia is not obtained with a 600-mcg dose, the next titration step is 800 mcg.

During titration, patients can be instructed to use multiple dosage strengths for any single dose. Patients should be instructed not to use more than four tablets at one time.

Dose proportionality between 800 mcg and 1,600 mcg in C_{max} and AUC has been demonstrated in clinical trials. However, the efficacy and safety of doses higher than 800 mcg have not been evaluated in clinical studies in patients.

HOW SUPPLIED²⁶

Dosage Forms and Strengths

FST is supplied in six dosage strengths: 100, 200, 300, 400, 600, and 800 mcg. Tablets are supplied in child-resistant, protective blister cards with peelable foil. Each blister card contains four tablets in pack sizes of 32 (all strengths) tablets.

Each tablet is white, with the strength distinguishable by the shape of the dosage unit and by debossing on the tablet surface. FST adheres to the FDA's definition of a sugar-free substance (i.e., it does not lower plaque pH below 5.7)²⁹; granulated mannitol is used as the carrier material.²²

The Abstral REMS Program

FST (Abstral) is a Schedule II controlled substance with a potential for abuse similar to that of other opioid analgesics. Because of the risk of misuse, abuse, addiction, and overdose, FST is available only through the FDA-mandated Abstral REMS (Risk Evaluation and Mitigation Strategy) program, a restricted distribution program.

Under this program, pharmacies, distributors, and health care professionals who prescribe this product to outpatients are required to enroll in the program to prescribe, dispense and distribute the drug. The FDA has standardized key components of the REMS program, including a patient–prescriber agreement and an enrollment form, to facilitate the adoption of a single shared system. These components can be used by all sponsors of immediate-release transmucosal fentanyl products to develop individual REMS programs such as the program

approved for FST. The FDA has also directed the sponsors of this class of products to work together on a single shared system to implement the REMS.²⁶

An overview of the requirements for prescribers, pharmacies, patients, and distributors is included as follows:

- Health care professionals who prescribe FST for outpatient use must review the prescriber educational materials, enroll in the program, and successfully complete the Prescriber Knowledge Assessment.
- To receive FST, outpatients must understand the risks and benefits of the drug and sign a patient–prescriber agreement with their health care provider. Outpatients will be enrolled by the pharmacy at the time their first prescription is filled.
- Outpatient pharmacies that dispense FST for outpatient use must enroll in the program, train their pharmacy staff on the REMS requirements, and successfully complete the Pharmacy Knowledge Assessment.
- Inpatient pharmacies that dispense FST for inpatient use must enroll in the program, train their pharmacy staff on the REMS requirements, and successfully complete the Pharmacy Knowledge Assessment.
- Wholesalers and distributors that distribute FST must enroll in the program and commit to distributing only to authorized enrolled pharmacies.

Health care providers who prescribe FST for inpatient use only are not required to enroll in the Abstral REMS program. Patients in an inpatient setting (e.g., hospitals, hospices, or long-term care facilities) are not required to enroll in the Abstral REMS program.

In an outpatient setting, health care professionals and pharmacists are provided copies of FST medication guides to use in the counseling of patients on safe and effective use of FST. A medication guide is provided to the patient each time FST is dispensed, as required by law.

As with all Schedule II drugs, a new prescription is required each time the prescription is filled. An electronic verification pharmacy management system will confirm that the prescriber, participating pharmacy, and patient are all enrolled in the Abstral REMS program.

The Abstral REMS program provides educational and enrollment materials to prescribers and pharmacies via the Web site at www.abstralrems.com and through the call center, 1-888-227-8725 (1-888-ABSTRAL).

Conclusion

The management of pain in patients with cancer is a significant challenge to clinicians. Suboptimal pain management affects a large proportion of patients and contributes to diminished quality of life, high levels of functional disability in various life domains, and emotional distress. A number of studies have established that patients experiencing breakthrough pain (BTP) report a significantly greater negative impact of pain on their level of activity, mood, ability to walk, work performance, social relationships, sleep, and enjoyment of life, compared with patients who do not experience BTP. In addition, BTP is associated with higher levels of negative emotional effects, including depression and anxiety.

Treatment guidelines for cancer pain recommend different interventions according to the nature and classification of pain, important distinctions made for nociceptive and neuropathic pain, pain intensity, and BTP among opioid-naïve and opioid-tolerant patients. Guideline-recommended therapies for pain management require individualized treatment plans and ongoing assessments to ensure that optimal levels of relief are obtained with minimal side effects.

For patients with cancer, BTP is a particular challenge for clinicians because of its rapid onset, its intensity, and, frequently, the lack of information about precipitating events that characterize this type of pain. The recommendations for optimal control of BTP emphasize the rapid action of the pharmacological effects of medications to effectively manage the sudden onset, severity, and frequency of BTP episodes.

Abstral, a fentanyl sublingual tablet (FST), is an effective therapy for BTP among opioid-tolerant patients with cancer. The efficacy of FST has been established in a phase 2 trial and in two phase 3 trials that used multiple, clinically relevant measures including sum of pain intensity difference (SPID), pain intensity difference, pain

relief, overall pain response, and patient ratings of satisfaction with pain relief compared with placebo.

In the most recent study, the Patients' Global Evaluation of Medication (PGEM), the Brief Pain Inventory (BPI), and the Depression, Anxiety, and Positive Outlook Scale (DAPOS) were used to assess effectiveness.

Administration of FST is a noninvasive intervention. No discomfort is associated with its administration. It is simple for patients and caregivers to administer and serves as a practical alternative to parenteral interventions, particularly for patients who cannot tolerate the parenteral route of administration.¹⁹

FST is rapidly absorbed; it has less variation in therapeutic efficacy and a faster onset of action compared with other routes of opioid administration as a result of the direct delivery of active drug to the central circulation, thereby eliminating the need for gastric or hepatic metabolism. The rapid absorption is a therapeutic priority for the management of BTP, and *in vitro* tests revealed that the tablets disintegrate in less than one minute.

FST does not provoke local irritation at the site of oral administration, even though this is a frequently reported adverse event reported for some alternative formulations of submucosal fentanyl. Unlike fentanyl citrate oral transmucosal lozenge (Actiq), which contains approximately two grams of sugar per unit, FST is sugar-free; the drug's carrier material is granulated mannitol.

FST is generally well tolerated by most patients, with side effects similar to those of other opioids and with little evidence of local irritation, such as oral ulcerations, pain, or edema. This product offers clinicians and their patients rapid, effective relief of BTP with few side effects beyond what is typically seen with opioid medications.

The full prescribing information for FST can be accessed via the Web site at www.abstral.com.

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