

Original Article

A Prospective, Single-Cohort, Open, Multi-Center, Observational Study of Sublingual Fentanyl for Breakthrough Cancer Pain: Effectiveness, Safety, and Tolerability in Korean Cancer Patients

Youn Seon Choi^{1,*}, Su-Jin Koh^{2,*}, Woo Kyun Bae³, Se Hyung Kim⁴, Seong Hoon Shin⁵, So Yeon Oh⁶, Sang Byung Bae⁷, Yaewon Yang⁸, Eun-Kee Song⁹, Yoon Young Cho¹⁰, Pyung Bok Lee¹¹, Ho-Suk Oh¹², MinYoung Lee¹³, Jin Seok Ahn¹⁴

*Youn Seon Choi and Su-Jin Koh contributed equally to this work.

Correspondence: Jin Seok Ahn

Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-Ro Gangnam-gu, Seoul 06351, Korea

Tel: 82-2-3410-3459

E-mail: Jinseok.ahn@samsung.com

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as an 'Accepted Article', [doi:10.4143/crt.2024.557](https://doi.org/10.4143/crt.2024.557)

¹Department of Family Medicine, Korea University Guro Hospital, Seoul, ²Department of Hematology and Oncology, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, ³Department of Internal Medicine, Chonnam National University Medical School, Hwasun, ⁴Division of Hematology and Oncology, Soonchunhyang University Hospital, Bucheon, Bucheon, ⁵Department of Internal Medicine, Kosin University Gospel Hospital, Busan, ⁶Department of Internal Medicine, Pusan National University Yangsan Hospital, Pusan National University Medical School, Yangsan, ⁷Department of Internal Medicine, Soonchunhyang University Cheonan Hospital, Cheonan, ⁸Department of Internal Medicine, Chungbuk National University Hospital, Chungbuk National University, College of Medicine, Cheongju, ⁹Department of Internal Medicine, Jeonbuk National University Medical School, Jeonju, ¹⁰Division of Hematology/Oncology, Department of Internal Medicine, Daegu Catholic University School of Medicine, Daegu, ¹¹Department of Anesthesiology and Pain Medicine, Seoul National University Bundang Hospital, Seongnam, ¹²Department of Hematology and Oncology, Gangneung Asan Hospital, University of Ulsan College of Medicine, Gangneung, ¹³A.Menarini Korea Ltd., Seoul, ¹⁴Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Abstract

Purpose

Fentanyl, a highly lipophilic opioid, was developed as a sublingual fentanyl tablet (SFT) for the management of breakthrough cancer pain (BTcP), and its efficacy and safety were confirmed in a randomized, controlled study. We investigated the effectiveness and safety of SFT administered to alleviate BTcP in a real-world setting.

Materials and Methods

In this prospective, open, single-cohort study, conducted in 13 referral hospitals in South Korea, opioid-tolerant cancer patients receiving around-the-clock opioids for persistent cancer pain were enrolled if the individual had BTcP ≥ 1 episode/day during the preceding week. The primary outcome was the SFT titration success rate.

Results

Among 113 patients evaluated for effectiveness, 103 patients (91.2%) had a successful titration of SFT, with an effective dose range between 100 μ g and 400 μ g. The most frequent dose was 100 μ g, administered to 65.0%, 72.1%, and 81.8% of the patients at Week 1, 4, and 12, respectively. The proportion of patients achieving the personalized pain goal assessed in the first week was 75.2%. The mean change in pain intensity measured with a numeric rating scale at 30 and 60 minutes after taking SFT was -2.57 and -3.62, respectively ($p < 0.0001$ for both). The incidence rate of adverse events related to SFT among 133 patients included for safety evaluation was 9.0% (12/133), which included vomiting (3.0%), nausea (2.3%), and headache (1.5%).

Conclusion

In a real-world setting, SFT provides rapid and effective analgesia in BTcP, even at the lowest dose (100 μ g), and the safety profile was acceptable.

Key Words

Cancer Pain, Breakthrough pain, Fentanyl, Analgesics, Opioid, Pain measurement, Administration, Sublingual, Sublingual absorption

Accepted Article

Introduction

Breakthrough cancer pain (BTcP) is a transient exacerbation of pain occurring on a background of stable, persistent pain in cancer patients [1]. Usually, BTcP has a rapid onset and does not last long, but its intensity is severe [2]. Because of the lack of a unified definition, the exact prevalence of BTcP is hard to estimate [3-5]. However, published data suggest that BTcP can be experienced by up to 89% of cancer patients [1,6-10].

Given its detrimental effect on the quality of life, BTcP constitutes an important therapeutic target [1,11]. The primary treatment strategy nowadays is the combination of long-acting analgesics administered around-the-clock (ATC) to adequately control the background pain with immediate-release opioids as a rescue medication in the case of a BTcP episode [12]. While immediate-release opioids are effective and their dose can be adjusted by the patient, many of those drugs are hydrophilic, which delays the onset of their effect [6,13,14].

The abovementioned limitation was overcome by developing highly lipophilic opioids, absorbed through the oral mucosa and producing rapid-onset analgesia without undergoing the first-pass metabolism. Fentanyl is a highly lipophilic opioid suitable for oral transmucosal administration [6,11]. The agent is available in various formulations, among them as oral transmucosal fentanyl citrate (OTFC), fentanyl buccal tablet and fentanyl buccal soluble film [15–17]. Another form of transmucosal fentanyl is a sublingual fentanyl tablet (SFT) marketed as Abstral (A.Menarini Korea, Ltd.). SFT reaches its peak blood concentrations within 10 minutes of administration, providing rapid-onset analgesia [18]. Long-term effectiveness and tolerability of SFT in the control of BTcP has already been confirmed in two phase III trials involving opioid-tolerant cancer patients, and the safety profile of the drug was shown to be similar as for other rapid-onset opioids [19,20].

This prospective observational study was designed to verify the abovementioned findings in a real-world setting, using less stringent criteria than in randomized clinical trials. The aim of the study was to analyze the effectiveness, safety and tolerability of SFT in the control of BTcP in a cohort of Korean cancer patients.

Materials and Methods

1. Study design

This was an observational, prospective, open, single-cohort study conducted in 13 referral hospitals in South Korea. Patients who were prescribed SFT, marketed as Abstral (A.Menarini Korea, Ltd.), for BTcP were followed up for twelve weeks to collect data mainly regarding SFT dose titration, pain intensity, quality of life, and adverse events in a real-world clinical setting. The study was registered at ClinicalTrials.gov (identifier: NCT03895762).

2. Participants

An adult male or female cancer patient aged 19 years or older for whom SFT was indicated for uncontrolled BTcP was invited to the study. After obtaining written informed consent, the following eligibility criteria were confirmed: (1) history of previous unsuccessful treatment for BTcP with other fentanyl products based on the investigator's judgment or the patient's dissatisfaction; (2) BTcP ≥ 1 episode/day during the week preceding the enrollment; (3) receiving ATC opioids for persistent cancer pain; and (4) opioid-tolerant, i.e. receiving, for more than a week, oral morphine ≥ 60 mg/day, fentanyl patch ≥ 25 μ g/hour, oxycodone ≥ 30 mg/day, oral hydromorphone ≥ 8 mg/day, or an equianalgesic dose of another opioid. Patients with the following conditions were excluded from the study: previous use of SFT within one

month before enrollment; contraindicated conditions for SFT; history of participation in an opioid-related clinical trial within 30 days before enrollment; or neuropathic pain.

3. Outcomes

The primary effectiveness endpoint was the SFT titration success rate. A titration was considered successful if all the following conditions were met: (1) no additional dose was administered during each maintenance phase (within two hours after taking SFT), (2) pain intensity reduction ≥ 2 points on the numeric rating scale (NRS) at 30 minutes post-dosing, and (3) adverse drug reactions, if any, were tolerable. As for secondary effectiveness endpoints, the following outcomes were examined: proportion of patients achieving personalized pain goal assessed via NRS at the first Week, SFT maintenance dose, maximum pain intensity among all incidences of BTcP, pain intensity difference at 30 and 60 minutes from the pre-dose score, Brief Pain Inventory (BPI) scores, and sleep quality measured as the number of awakenings during sleep. The relationship between SFT dose and ATC opioid dose was investigated as a post-hoc exploratory endpoint. For safety endpoints, treatment-emergent adverse events (TEAEs), blood pressure, and pulse rate were monitored. The severity of TEAEs were classified as mild, moderate, and severe based on their impact on daily activities. Mild TEAEs caused no interference with daily activities, while severe TEAEs resulted in a complete inability to perform daily activities. Seriousness and causality of TEAEs were assessed following the guidelines of International Conference on Harmonisation (ICH), ICH E2A and E2E, respectively.

4. Statistical analysis

The sample size of 262 was calculated to secure the precision of the confidence interval (CI) for the primary endpoint (assumed as 64.4%) at the width of 0.12. The success rate of the primary endpoint was referenced in the previous study [21]. A total of 309 patients were targeted for enrollment, assuming a 15.0% drop-out rate.

The safety set comprised all enrolled patients who took at least a single dose of SFT and had safety follow-up data. Among patients included in the safety set, those with at least one effectiveness datum were included in the effectiveness set. Study data were summarized primarily with descriptive statistics. Mean, standard deviation (SD), median, and ranges (minimum, maximum, and interquartile range) were presented for continuous variables. Multiple categorical or dichotomous variables were summarized with the number of patients and percentage. The titration success rate and proportion of patients achieving pain goals were also presented with 95% CIs. The relationship between SFT dose and ATC opioid dose was tested using Pearson's correlation coefficient test. Differences in pain intensity between post-dosing (30 and 60 minutes after dosing) and pre-dosing were tested with Wilcoxon signed rank test. BPI scores at follow-up visits were compared with the baseline or Week 1 score using repeated measures analysis of variance. Additional details of study design, procedures, and statistical analysis were published previously [22].

Results

1. Participants

During the period between 4 July 2017 and 28 June 2019, 143 patients who received SFT for breakthrough cancer pain were screened for the study, 136 were enrolled, and 36

completed the 12-week follow-up study schedule (Fig. 1). Although just about half of the planned number of patients were enrolled, the enrollment was not extended as to finish the study within the period approved by the institutional review boards. The most common reason for early withdrawal was death (31.0%) followed by consent withdrawal (24.0%), lost to follow-up (18.0%), and physician's discretion (18.0%). After excluding patients without available data, 133 and 113 patients, respectively, were included in the safety and effectiveness sets. Mean (SD) age was 60.37 (11.54) years, with 36.8% being at least 65 years old or older (Table 1). More male patients were enrolled (63.2% vs. 36.8%), and the mean (SD) body mass index (BMI) was 21.60 (3.11) kg/m². Primary cancers diagnosed in more than 10% of patients within five years prior to the study enrollment were, in the order of frequency, head and neck cancer (15.0%), pancreatic cancer (12.0%), and colorectal cancer (11.3%). As treatment for cancer, 91.7% of the patients received chemotherapies, 42.9% surgical operations, and 35.3% radiotherapies. Patients mostly marked the front torso (62.8%), back torso (46.0%), or front side of head/neck/shoulder (26.5%) as painful areas, and these responses were consistent with the most painful areas (Table 2). Baseline ATC opioid dose (mg/day in oral morphine equivalent) was distributed most frequently between 100 mg (inclusive) and 400 mg (exclusive) (53.9%), and 19.5% of patients were receiving ATC opioid $\geq$ 400 mg among 128 patients with available data (mean (SD) = 277.80 (248.68) mg). The most frequently used concomitant opioid was fentanyl patch (78.9%), followed by oxycodone (44.5%), tramadol (14.1%), and morphine (13.3%).

2. Effectiveness

Among 113 patients in the effectiveness set, 103 had a successful SFT titration. Hence,

the titration success rate was 91.2% (95% CI: 85.9%; 96.4%). The majority of the patients (n=100) obtained successful titration of SFT by Week 1, and three more patients reached it by Week 4 (Fig. 2A). Initial titration dose and subsequent maintenance dose of SFT ranged from 100 µg to 400 µg, and the most frequently used dose was 100 µg (Fig. 2B). The proportions of patients using 100 µg of SFT were 65.0%, 72.1%, and 81.8% at Week 1, 4, and 12, respectively. The proportions of patients who used 300 µg or 400 µg of SFT were less than 10% across all timepoints (4-9%). Meanwhile, the mean ATC opioid dose (mg/day in oral morphine equivalent) gradually increased over time, with mean doses of 292 mg, 385 mg, 526 mg, and 529 mg at baseline, Week 1, Week 4, and Week 12, respectively. The increased mean dose of ATC opioids at later time points was contributed mainly by the increased dose of long-acting opioids, with mean doses of 289 mg, 377 mg, 533 mg, and 526 mg at baseline, Week 1, Week 4, and Week 12, respectively, whereas mean doses of short-acting opioids were 25 mg, 34 mg, 28 mg, and 27 mg, respectively, at the same time points. Statistically significant correlations were observed between the mean ATC opioid dose and maintenance dose of SFT (Pearson's correlation coefficient 0.21, p=0.03) as well as between mean ATC opioid dose and final dose of SFT (Pearson's correlation coefficient 0.25, p=0.01); however, the levels of correlation were too weak to bear a clinical significance.

The target pain goal set by each patient at baseline ranged from score 0 to 5 on an 11-point NRS, where 0 represented no pain. Specifically, 19.5% of patients set a NRS goal of 0, 15.9% of 1, 16.8% of 2, 36.3% of 3, 6.2% of 4, and 5.3% of 5. At Week 1, the proportion of patients achieving the personalized pain goal assessed with NRS was 75.2% (95% CI: 67.3%; 83.2%). The total number of incidences of BTcP per patient during the first week of the study ranged from 1 to 41, with a median of 9. Among all incidences of BTcP recorded on the pain

diary during the first week of the study, maximum pain intensity on the NRS ranged from 7 to 10 (interquartile range: 9-10), and its mean (SD) was 9.37 (0.84). Mean (SD) of BTcP intensity right before taking SFT was 6.14 (1.68), and SFT resulted in significant reduction in the pain (Fig. 3). Mean (SD) change in pain intensity at 30 and 60 minutes after taking SFT was -2.57 (1.53) and -3.62 (1.89), respectively ($p < 0.0001$ for both).

The number of awakenings during sleep was recorded on the pain diary during the first week of the study, and its mean (SD) frequency was 1.70 (1.20) times/day.

Responses on the BPI questionnaire showed that the worst pain within the previous 24 hours (NRS mean) was reduced from baseline (7.21) at Week 1 (6.62, $p = 0.0346$) and Week 4 (6.50, $p = 0.0290$) but no statistical difference was found at Week 12 (6.83, $p = 0.3776$). NRS mean of least pain within the previous 24 hours at baseline was 2.29, and thereafter, the mean values ranged from 2.16 to 2.63. NRS mean values of average and current pain ranged from 3.58 to 4.21 and 2.92 to 3.40, respectively. The median of pain relief (%) from pain medication used within 24 hours at baseline was 50% (interquartile range 30-70%), and median values and interquartile ranges at later visits implied the level of pain relief modestly increased with time (e.g., at Week 4, median 60%; interquartile range 50-80%); however, no statistical difference was detected. In terms of pain interference with daily activities, general trend of improvement in quality of life was observed till Week 12 and the BPI scores were lowest at Week 4 (Fig. 4). Compared with baseline BPI score, mean BPI scores of general activity at Week 4 (7.09 vs. 6.17, $p = 0.0155$), mood at Week 4 (7.07 vs. 5.91, $p = 0.0045$), normal work at Week 4 and 12 (7.14 vs. 6.02_[Week 4], $p = 0.0052$; vs. 6.10_[Week 12], $p = 0.0475$), relations with other people at Week 4 (6.38 vs. 5.31, $p = 0.0152$), sleep at Week 1, 4, and 12 (6.04 vs. 5.20_[Week 1], $p = 0.0402$; vs. 4.11_[Week 4], $p < 0.0001$; vs. 4.70_[Week 12], $p = 0.0326$), and enjoyment of life at Week 4 (6.77 vs.

5.53, $p=0.0041$) were lower with statistical significance. Furthermore, mean BPI scores of normal work, sleep, and enjoyment of life in Week 4 were lower than in Week 1 with statistical significance ($p=0.0461$, $p=0.0247$, and $p=0.0379$, respectively).

3. Safety

Among 133 patients, 91 (68.4%) experienced 268 TEAEs, of which 171, 61, and 36 events were respectively mild, moderate, and severe in severity. The most common TEAEs were gastrointestinal symptoms (Table 3). A total of 24 TEAEs were reported to have fatal outcomes, most of which were due to exacerbation of the underlying diseases. Two TEAEs, which were confusional state and vomiting, reported in two patients led to permanent discontinuation of SFT. According to the investigator's assessment of the causality of TEAEs, 19 events reported in 12 patients (9.0%) were classified as adverse drug reactions (probable/likely = 1 event, possible = 9 events, conditional/unclassified = 2 events, and unassessable/unclassifiable = 7 events). The most common adverse drug reactions were vomiting (4 events) and nausea (3 events). Six serious adverse drug reactions (hepatocellular carcinoma, nasal sinus cancer, dyspepsia, multiple organ dysfunction syndrome, oral candidiasis, and headache) were reported in five patients. No clinically significant findings or statistically significant changes were detected in blood pressure or pulse rate.

Discussion

The aim of the present study was to analyze the effectiveness, safety and tolerability of SFT in Korean cancer patients with BTcP. Most of the study patients successfully completed the titration phase, with effective doses of SFT of 100-400 μg . SFT provided rapid analgesia,

which, aside from a significant reduction in BTcP severity, also contributed to an improvement in the quality of life. SFT was generally tolerated well, with a safety profile similar to other transmucosal fentanyl formulations.

The titration success rate in the present study (91.2%) differed considerably from the results of two published randomized trials evaluating the efficacy and tolerability of SFT for the treatment of BTcP in opioid-tolerant cancer patients (59.5% and 69.1%) [19,20]. Titration success rates in clinical trials of other transmucosal fentanyl formulations, OTFC, fentanyl buccal tablet and fentanyl buccal soluble film, were also different from the present study, with the effective doses obtained in 71%, 65%, and 54% of patients, respectively [15-17]. The high titration success rate in our present study seems to be primarily related to its real-world character. In the two trials of SFT mentioned above [19,20], primary reasons behind the titration phase failure were administrative factors, such as protocol violation, the sponsor's decision or the subject's withdrawal of consent. After excluding those factors, which do not play a role in real-world clinical practice, the proportions of patients who completed the titration phase in those two trials would be similar as in the present study, at 80.1% and 84.2% [19,20].

In the present study, the effective dose of SFT, defined as the single dosage strength providing effective relief (pain reduction ≥ 2 on NRS) of all BTcP episodes with an acceptable and tolerable AE profile, was 100-400 μg , with the most frequently used dose being 100 μg . A similar definition of effective dose was also used in the previously mentioned randomized, placebo-controlled, multicenter phase III trial of SFT [19]. In that study, effective analgesia was achieved at a broader SFT dose strength spectrum, 100-800 μg , with the effective dose ≥ 300 μg for over 85% of patients [19]. Similar dose distributions were also reported in the studies analyzing other transmucosal fentanyl formulations, OTFC, fentanyl buccal tablet and

fentanyl buccal soluble film [15-17]. However, those studies used less stringent effective dose definitions, with no relief of all BTcP required, which precludes a head-to-head comparison of their results with our findings [21]. Thus, it is unclear if the difference between the effective dose spectra of SFT in the present real-world study and the previous clinical trial is associated with different patient characteristics or whether it is clinically relevant [19]. Nevertheless, having a choice between dosing strengths, clinical practitioners should select the one that provides an optimal balance between analgesic effects and acceptable adverse effects in a given patient.

At 30 and 60 minutes after administration of SFT, our patients reported significant pain reduction, expressed as a pain intensity difference compared to the pre-dose pain. Hence, the study confirmed that SFT can provide a rapid analgesic effect during a BTcP episode. This observation is consistent with the data from the multicenter phase III trial of SFT [19]. In that study, the mean sum of pain intensity difference at 30 and 60 minutes after the administration of SFT was significantly greater than with placebo. Additionally, the administration of SFT was associated with significantly greater improvements in pain intensity difference and significantly greater pain relief, starting 10 minutes post-dose and lasting throughout the 60-minute assessment period [19].

Our analysis showed the absence of a strong correlation between the mean ATC opioid dose and SFT dose. The results of previous studies in this matter are inconclusive. While some authors found a moderate to strong correlation between ATC opioid dose and the effective dose of OTFC [23,24], many others observed weak correlations between those variables or no correlations at all [25-28]. One important aspect that needs to be considered when using SFT for BTcP is starting titration with the lowest dose of the drug to avoid unnecessary side effects,

as recommended in the current label of the product. Most of our patients could manage BTcP with the lowest dose (100 µg), which might explain a weak correlation between the ATC opioid dose and the final or maintenance dose of SFT documented in the present study.

Up to 75.2% of patients participating in the present study reached their target goal of pain level. The analysis of the BPI scores in the sensory dimension adds to this observation, showing that the worst pain within the previous 24 hours (NRS mean) was significantly reduced from baseline at Weeks 1 and 4. The lack of significant difference in NRS mean at Week 12 was likely associated with 73.5% of patients being withdrawn prematurely, mostly due to high mortality, which made the sample underpowered. Nevertheless, the results of the non-randomized, open-label, multicenter phase III study, with a maintenance phase lasting up to 12 months [20], suggest that SFT can also be effective in a longer perspective. In that trial, mean pain levels generally remained stable throughout the 12-month follow-up period, and the current pain level at six months was even significantly lower than at the baseline [20].

Published evidence suggests that merely a modest correlation exists between pain intensity and everyday functioning [29]. In this context, our findings for the reactive dimensions of BPI are worth emphasizing. In the present study, the scores for the reactive dimensions of BPI generally decreased with time, in some cases significantly, with the lowest values observed at Week 4. Especially, the interference of sleep due to pain was significantly improved at all timepoints. Similar to the sensory dimension, the lack of significant improvement in most reactive dimensions of the BPI at Week 12 might be associated with the low statistical power of the sample at this time point. In the adequately powered multicenter phase III study [20], the composite score for interference of pain with daily activities was significantly improved at six months, and so were five out of seven individual aspects of this dimension. The same study

showed that analgesia achieved with SFT exerted a favorable effect on other dimensions of the quality of life, measured with the depression, anxiety and positive outlook scale (DAPOS) [20]. Taken altogether, both our findings and the published evidence show that the analgesic effect of SFT is also associated with a beneficial effect on the quality of life.

In this study, 268 TEAEs were recorded in 91 out of 133 patients (68.4%), with the vast majority (232 out of 268 events) being mild or moderate in severity. A total of 19 events reported in 12 patients (9.0%) were classified as adverse drug reactions, with the most common being vomiting and nausea. This safety profile was similar to those reported previously in the phase III trials of SFT [19,20]. In those studies, AEs were documented in 43.3% of the patients and were predominantly mild or moderate in severity. The most common AEs were nausea (12.2%), vomiting (5.3%) and somnolence (4.3%) [21]. The pattern of AEs documented in the present study was also consistent with those reported in the trials of other transmucosal fentanyl preparations and rapid-onset opioids [16,21].

The primary limitation of this study is associated with a high withdrawal rate, which is unfortunately unavoidable in the case of research involving terminally ill patients. Also, the short duration of the study did not allow us to analyze the long-term effectiveness, safety and tolerability of SFT. To address these limitations in future research, larger sample sizes and longer study durations could be considered. Leveraging the analysis of the large-scale data set, such as the electronic medical records or health claims data, could provide valuable insights into real-world effectiveness. Despite some shortcomings mentioned above, the results of the present study are valuable from the practical point of view because of its real-world character. Because of less stringent eligibility criteria, participants of this study were probably more representative of the population of cancer patients suffering from BTcP than subjects included

in previous phase III trials of SFT. Moreover, all treatment-related decisions were left solely at the investigator's discretion, allowing us to analyze the treatment outcomes in various clinical scenarios unlikely to be tested in a traditional clinical trial.

To summarize, the results of this real-world study stay in agreement with the evidence from previous phase III trials, showing that SFT provides rapid and effective analgesia in BTcP without compromising the patient's safety.

Ethical Statement

The study protocol and the related documents were reviewed and approved by the institutional review board (IRB) of each participating study center. IRB approval numbers are listed below. All study participants provided a written informed consent before enrollment in the study. The study was conducted in accordance with the principles of Declaration of Helsinki and Good Clinical Practice.

IRB approval numbers: Korea University Guro Hospital, 2017GR0002; Ulsan University Hospital, UUH2017-04-013-015; Chonnam National University Medical School, CNUHH-2017-066; Soonchunhyang University Hospital Bucheon, SCHBC2017-04-018-014; Kosin University Gospel Hospital, KUGH2017-04-037-013; Pusan National University Yangsan Hospital, 02-2017-014; Soonchunhyang University Cheonan Hospital, SCHCA2017-04-021-016; Chungbuk National University Hospital, CBNUH2017-04-007-012; Jeonbuk National University Medical School, CUH2017-05-016-017; Daegu Catholic University School of Medicine, CR-17-049-L; Seoul National University Bundang Hospital, B-1712-438-306; Gangneung Asan Hospital, GNAH2018-01-006-010; and Samsung Medical Center, SMC2017-04-127-015.

Author Contributions

Conceived and designed the analysis: Choi YS, Lee MY, Ahn JS.

Collected the data: Choi YS, Koh SJ, Bae WK, Kim SH, Shin SH, Oh SY, Bae SB, Yang Y, Song EK, Cho YY, Lee PB, Oh HS, Ahn JS.

Contributed data or analysis tools: Choi YS, Koh SJ, Lee MY, Ahn JS.

Performed the analysis: Lee MY, Ahn JS.

Wrote the paper: Choi YS, Koh SJ, Bae WK, Kim SH, Shin SH, Oh SY, Bae SB, Yang Y, Song EK, Cho YY, Lee PB, Oh HS, Lee MY, Ahn JS.

Review and interpretation: Choi YS, Koh SJ, Bae WK, Kim SH, Shin SH, Oh SY, Bae SB, Yang Y, Song EK, Cho YY, Lee PB, Oh HS, Lee MY, Ahn JS.

ORCID iDs

Youn Seon Choi: <https://orcid.org/0000-0003-2406-5848>

Su-Jin Koh: <https://orcid.org/0000-0002-1545-8036>

Jin Seok Ahn: <https://orcid.org/0000-0002-2880-6730>

Conflicts of Interest

Dr. Jin Seok Ahn received payments for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Nokwon Medical, Boryung, Yuhan, Takeda Pharmaceuticals, Samyang, Pfizer, Boehringer Ingelheim, Bayer Korea, BC World, Roche Korea, AstraZeneca Korea, Novartis Korea, Amgen Korea, Lilly Korea, Kyowa Kirin, and Hanmi. Dr. Jin Seok Ahn also participated on a Data Safety Monitoring Board or Advisory

Board of Daiichi Sankyo Korea, ImmuneOncia, Therapex, Bayer Korea, Vifor Pharma, Pharmbio Korea, Roche, Yuhan, and Yooyoung Pharmaceutical. Ms. MinYoung Lee is a full-time employee of A.Menarini Korea.

Funding

The work was supported by A.Menarini Korea, the marketing authorization holder of Abstral in Korea.

References

1. Portenoy RK, Hagen NA. Breakthrough pain: definition, prevalence and characteristics. *Pain*. 1990;41:273–81.
2. Davies A, Buchanan A, Zeppetella G, Porta-Sales J, Likar R, Weismayr W, et al. Breakthrough cancer pain: an observational study of 1000 European oncology patients. *J Pain Symptom Manage*. 2013;46:619–28.
3. Haugen DF, Hjermstad MJ, Hagen N, Caraceni A, Kaasa S. Assessment and classification of cancer breakthrough pain: a systematic literature review. *Pain*. 2010;149:476–82.
4. Boceta J, De la Torre A, Samper D, Farto M, Sánchez-de la Rosa R. Consensus and controversies in the definition, assessment, treatment and monitoring of BTcP: results of a Delphi study. *Clin Transl Oncol*. 2016;18:1088–97.
5. Davies AN, Elsner F, Filbet MJ, Porta-Sales J, Ripamonti C, Santini D, et al. Breakthrough cancer pain (BTcP) management: a review of international and national guidelines. *BMJ Support Palliat Care*. 2018;8:241–9.
6. Hong SH, Roh SY, Kim SY, Shin SW, Kim CS, Choi JH, et al. Change in cancer pain management in Korea between 2001 and 2006: results of two nationwide surveys. *J Pain Symptom Manage*. 2011;41:93–103.
7. Deandrea S, Corli O, Consonni D, Villani W, Greco MT, Apolone G. Prevalence of breakthrough cancer pain: a systematic review and a pooled analysis of published literature. *J Pain Symptom Manage*. 2014;47:57–76.
8. Baek SK, Kim DY, Kang SY, Sym SJ, Kim YS, Lee JY. A Korean Nationwide Survey for Breakthrough Cancer Pain in an Inpatient Setting. *Cancer Res Treat*. 2016;48:768–

- 74.
9. Mercadante S. Breakthrough pain in cancer patients: prevalence, mechanisms and treatment options. *Curr Opin Anaesthesiol.* 2015;28:559–64.
10. Pérez-Hernández C, Blasco A, Gándara Á, Mañas A, Rodríguez-López MJ, Martínez V, et al. Prevalence and characterization of breakthrough pain in patients with cancer in Spain: the CARPE-DIO study. *Sci Rep.* 2019;9:17701.
11. Caraceni A, Martini C, Zecca E, Portenoy RK, Ashby MA, Hawson G, et al. Breakthrough pain characteristics and syndromes in patients with cancer pain. An international survey. *Palliat Med.* 2004;18:177–83.
12. Vellucci R, Mediatì RD, Gasperoni S, Mammucari M, Marinangeli F, Romualdi P. Assessment and treatment of breakthrough cancer pain: from theory to clinical practice. *J Pain Res.* 2017;10:2147–55.
13. Simon SM, Schwartzberg LS. A review of rapid-onset opioids for breakthrough pain in patients with cancer. *J Opioid Manag.* 2014;10:207–15.
14. Løhre ET, Thronæs M, Klepstad P. Breakthrough cancer pain in 2020. *Curr Opin Support Palliat Care.* 2020;14:94–9.
15. Farrar JT, Cleary J, Rauck R, Busch M, Nordbrock E. Oral transmucosal fentanyl citrate: randomized, double-blinded, placebo-controlled trial for treatment of breakthrough pain in cancer patients. *J Natl Cancer Inst.* 1998;90:611–6.
16. Portenoy RK, Taylor D, Messina J, Tremmel L. A randomized, placebo-controlled study of fentanyl buccal tablet for breakthrough pain in opioid-treated patients with cancer. *Clin J Pain.* 2006;22:805–11.
17. Rauck R, North J, Gever LN, Tagarro I, Finn AL. Fentanyl buccal soluble film (FBSF)

- for breakthrough pain in patients with cancer: a randomized, double-blind, placebo-controlled study. *Ann Oncol.* 2010;21:1308–14.
18. Lennernäs B, Hedner T, Holmberg M, Bredenberg S, Nyström C, Lennernäs H. Pharmacokinetics and tolerability of different doses of fentanyl following sublingual administration of a rapidly dissolving tablet to cancer patients: a new approach to treatment of incident pain. *Br J Clin Pharmacol.* 2005;59:249–53.
 19. Rauck RL, Tark M, Reyes E, Hayes TG, Bartkowiak AJ, Hassman D, et al. Efficacy and long-term tolerability of sublingual fentanyl orally disintegrating tablet in the treatment of breakthrough cancer pain. *Curr Med Res Opin.* 2009;25:2877–85.
 20. Nalamachu S, Hassman D, Wallace MS, Dumble S, Derrick R, Howell J. Long-term effectiveness and tolerability of sublingual fentanyl orally disintegrating tablet for the treatment of breakthrough cancer pain. *Curr Med Res Opin.* 2011;27:519–30.
 21. Nalamachu SR, Rauck RL, Wallace MS, Hassman D, Howell J. Successful dose finding with sublingual fentanyl tablet: combined results from 2 open-label titration studies. *Pain Pract.* 2012;12:449–56.
 22. Choi YS, Koh SJ, Bae WK, Kim SH, Shin SH, Oh SY, et al. Observational study of efficacy, safety, and tolerability of fentanyl in Korean cancer patients (OASIS). *Med Case Reports Study Protoc.* 2021;2(3) [Epub]. https://journals.lww.com/md-cases/Fulltext/2021/03000/Observational_study_of_efficacy,_safety,_and.11.aspx
 23. Yen TY, Chiou JF, Chiang WY, Su WH, Huang MY, Hu MH, et al. Proportional dose of rapid-onset opioid in breakthrough cancer pain management: An open-label, multicenter study. *Medicine.* 2018;97:e11593.
 24. Chiou TJ, Chao TC, Chao TY, Huang JS, Chang YF, Wang CH. A dose titration study

- of fentanyl buccal soluble film for breakthrough cancer pain in Taiwan. *Cancer Rep.* 2019;2:e1179.
25. Kosugi T, Hamada S, Takigawa C, Shinozaki K, Kunikane H, Goto F, et al. A Randomized, Double-Blind, Placebo-Controlled Study of Fentanyl Buccal Tablets for Breakthrough Pain: Efficacy and Safety in Japanese Cancer Patients. *J Pain Symptom Manage.* 2014;47:990–1000.
26. Portenoy RK, Payne R, Coluzzi P, Raschko JW, Lyss A, Busch MA, et al. Oral transmucosal fentanyl citrate (OTFC) for the treatment of breakthrough pain in cancer patients: a controlled dose titration study. *Pain.* 1999;79:303–12.
27. Kress HG, Orońska A, Kaczmarek Z, Kaasa S, Colberg T, Nolte T. Efficacy and tolerability of intranasal fentanyl spray 50 to 200 microg for breakthrough pain in patients with cancer: a phase III, multinational, randomized, double-blind, placebo-controlled, crossover trial with a 10-month, open-label extension treatme. *Clin Ther.* 2009;31:1177–91.
28. Alberts DS, Smith CC, Parikh N, Rauck RL. Fentanyl sublingual spray for breakthrough cancer pain in patients receiving transdermal fentanyl. *Pain Manag.* 2016;6:427–34.
29. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain.* 2005;113:9–19.

Table 1. Patient demographics

Characteristics	Safety set (n=133)
Sex	
Male	84 (63.2)
Female	49 (36.8)
Age group, years	
21-34	2 (1.5)
35-49	20 (15.0)
50-64	62 (46.6)
≥65	49 (36.8)
BMI, kg/m²	
<18.5	18 (13.5)
18.5-25.0	84 (63.2)
25.1-29.9	15 (11.3)
≥30	1 (0.8)
ATC baseline opioid dose, MME^{a)}	
<100 mg	34 (26.6)
100-400 mg	69 (53.9)
≥400 mg	25 (19.5)
Concomitant opioids^{a)}	
Fentanyl patch	101 (78.9)
Oxycodone	57 (44.5)
Tramadol	18 (14.1)
Morphine	17 (13.3)
Hydromorphone	4 (3.1)
Others ^{b)}	10 (7.8)

Data are presented as number of patients (%). ATC, around-the-clock; BMI, body mass index; MME, morphine milligram equivalent. ^{a)}The number of patients with available data was 128.

^{b)}Others: codeine (n=8), buprenorphine (n=1), tapentadol (n=1).

Table 2. Area of pain based on the responses on the Brief Pain Inventory Questionnaire

	Area of pain (n=113)	Area of most strong pain (n=113)
Front head/neck/shoulder	30 (26.5)	26 (23.0)
Front torso	71 (62.8)	69 (61.1)
Front limbs	19 (16.8)	12 (10.6)
Back head/neck/shoulder	10 (8.8)	7 (6.2)
Back torso	52 (46.0)	41 (36.3)
Back limbs	10 (8.8)	7 (6.2)

Table 3. Common adverse events and adverse drug reactions

Adverse event at preferred term level	No. of patients (%) [No. of events]
Patients with adverse events	91 (68.4) [268]
Vomiting	14 (10.5) [14]
Multiple organ dysfunction syndrome	12 (9.0) [12]
Diarrhea	11 (8.3) [12]
Decreased appetite	10 (7.5) [10]
Nausea	9 (6.8) [10]
Constipation	8 (6.0) [8]
Dyspepsia	7 (5.3) [7]
Insomnia	7 (5.3) [7]
Patients with adverse drug reactions	12 (9.0) [19]
Vomiting	4 (3.0) [4]
Nausea	3 (2.3) [3]
Headache	2 (1.5) [2]

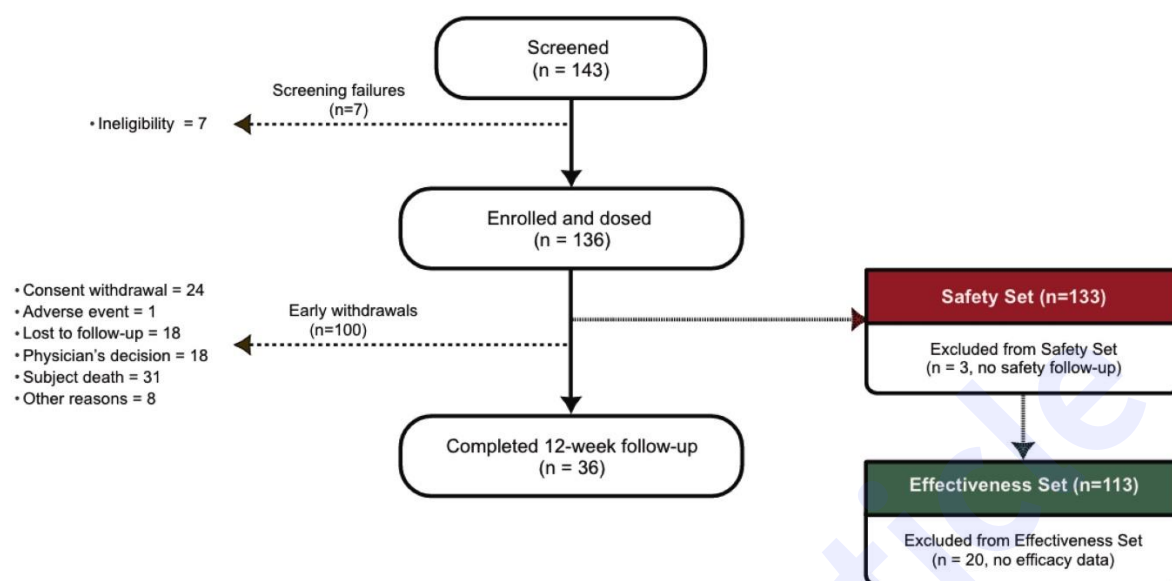


Fig. 1. Disposition of patients through the study.

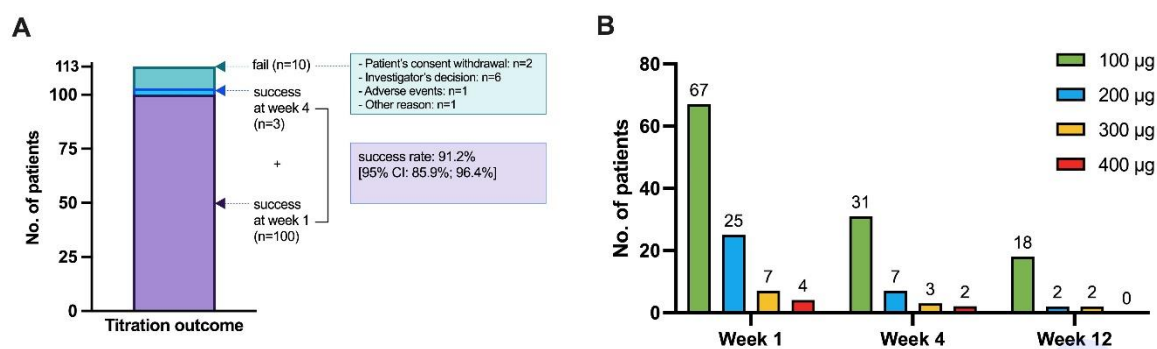


Fig. 2. Titration success rate (A) and the distribution of effective dose (B), in which initial titration doses of sublingual fentanyl tablet (SFT) are shown at Week 1, and subsequent maintenance doses are presented at Weeks 4 and 12. No patients were required to use 600 µg or 800 µg of SFT to resolve breakthrough cancer pain.

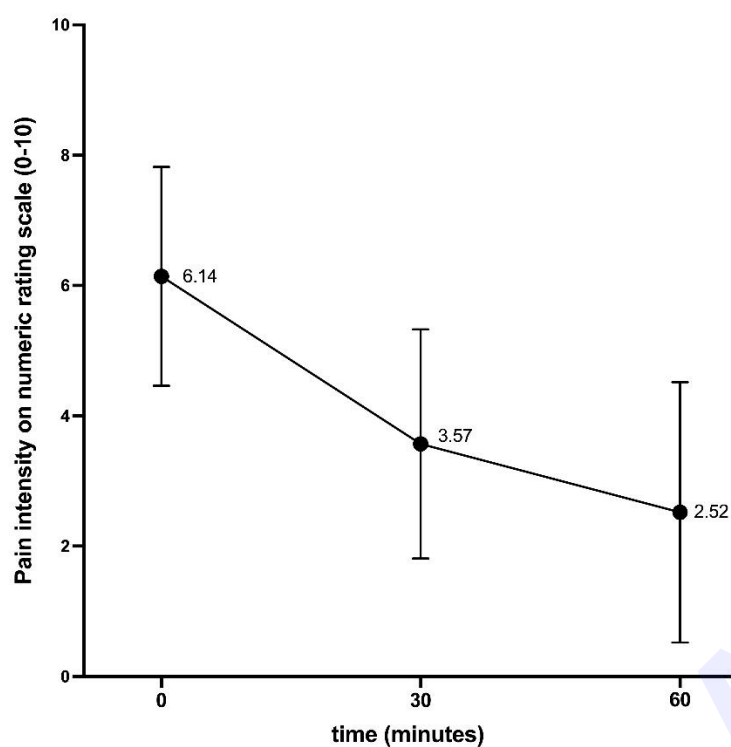


Fig. 3. Pain intensity changes after taking a sublingual fentanyl tablet (SFT) for breakthrough cancer pain. Data points are the mean (SD) of all recordings on the pain diaries from 105 patients at each time point. Time 0 = pre-dosing (right before taking SFT). The numeric rating scale (NRS) is 0 = no pain and 10 = worst pain.

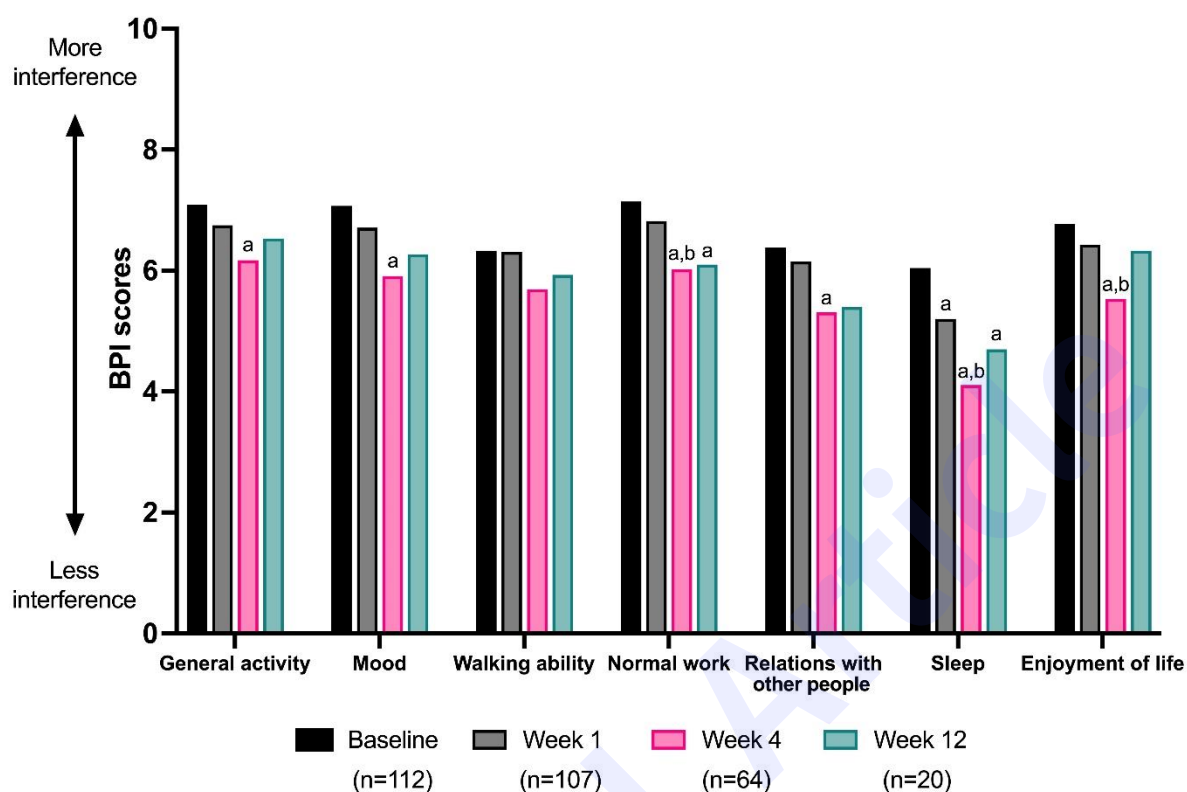


Fig. 4. Brief Pain Inventory (BPI) scores of reactive dimensions of pain. BPI score 0 = no interference, BPI score 10 = interferes completely. The height of each bar represents the mean BPI score, the level of interference on daily activities due to pain in a recall period of 24 hours at each time point. a, significantly ($p < 0.05$) different from baseline; b, significantly ($p < 0.05$) different from Week 1.