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ORIGINAL REPORT

Fentanyl Sublingual Tablets Versus Subcutaneous Morphine for the Management of Severe Cancer Pain Episodes in Patients Receiving Opioid Treatment: A Double-Blind, Randomized, Noninferiority Trial

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ABSTRACT

Purpose

Fentanyl sublingual tablets (FST) are a potentially useful alternative to parenteral opioids such as subcutaneous morphine (SCM) to treat severe cancer pain episodes. No direct comparison between FST and SCM is available. The aim of this study was to test noninferiority of FST versus SCM during the first 30 min postadministration.

Methods

Patients receiving stable opioid therapy and experiencing a severe pain episode were randomly assigned to either 100 μg FST or 5 mg SCM in a double-blind, double-dummy trial. Average pain intensity (PI) assessed on a 0 to 10 numerical rating scale at 10, 20, and 30 min postadministration was the main end point. Analysis of covariance, adjusted by baseline PI, was the main analysis. The noninferiority margin (NIm) for the between-group difference was set at −0.6, that is, equal to one third of the minimum clinically important PI difference of two points.

Results

A total of 114 patients were randomly assigned to either FST (n = 58) or SCM (n = 56). One patient (in the FST group) withdrew consent before drug administration and was excluded from analysis. Baseline mean PIs were 7.5 in both groups; mean average PIs assessed at 10, 20, and 30 min postadministration were 5.0 and 4.5 for FST and SCM, respectively, with the 95% CI of the between-group difference including the NIm (−0.49; 95% CI, −1.10 to 0.09). Patients taking FST received a second drug dose after 30 min more frequently than did patients taking SCM (51% *v* 37%, respectively; risk difference, −13%; 95% CI, −30% to 3%). Both treatments were well tolerated, with average follow-up adverse event scores below the response of "A Little." Ninety-three percent of patients preferred the sublingual administration.

Conclusion

This trial did not show noninferiority of FST versus SCM within the chosen NIm. Both treatments were safe, and patients preferred the sublingual route of administration. FST provides analgesia with modest to moderate increased risk of lower efficacy compared with SCM.

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INTRODUCTION

First-line therapeutic strategy for the control of moderate to severe cancer pain is around-the-clock opioid analgesic administration, as recommended by clinical practice guidelines.[1] However a considerable number of patients with cancer pain experience severe pain flares over an otherwise well-controlled background pain level.[2,3] Such episodes, usually described as incident pain, episodic pain, or breakthrough pain (BTP)[4-6] can significantly compromise overall pain control and patients' quality of life.[7]

Evidence-based guidelines recommend treating BTP with an as-needed (prn) prescription for immediate-release/short-acting opioids, in addition to long-acting/slow-release opioids used for background pain.[1] The use of oral immediate-release morphine has long been considered the gold standard medication for BTP.[1,8,9] Intravenous morphine or subcutaneous morphine (SCM) injections are also efficacious treatments for severe cancer pain episodes. They are safe and can ensure

ASSOCIATED CONTENT

Appendix
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rapid-onset pain relief,[1,10,11] with the intravenous route showing a more rapid action and the subcutaneous route offering wider practicability.[11]

More recently, several transmucosal fentanyl formulations (TFs), allowing rapid oral or nasal absorption, have been developed specifically to address BTP. When delivered in the bloodstream, fentanyl has short equilibration kinetics with the CNS compartment and is much faster than morphine, allowing a rapid onset of clinical effects.[12] The superior efficacy of these fentanyl delivery systems over placebo has been shown in various randomized controlled trials (RCTs).[13,14] TFs have also proved superior to immediate-release oral morphine in two double-blind[15,16] and in two open-label RCTs,[17,18] whereas comparison with parenteral morphine is limited to one open-label RCT study comparing oral fentanyl lozenges with intravenous morphine.[19] This study showed superior analgesia of morphine at 15 min and nonsignificant differences at 30 min.

In this study, we examined the analgesic effect of fentanyl sublingual tablets (FST; orally disintegrating tablets; Abstral; ProStrakan, Galashiels, United Kingdom), which were shown to be superior to placebo at 10, 15, 30, and 60 min post-treatment in a double-blind RCT[20] but were never directly compared with oral or parenteral morphine in RCTs.

The study rationale was built on the summary of clinical and pharmacologic experimental data suggesting that morphine concentration peaks within 1 hour after administration of immediate-release oral preparations[21,22] and that clinical effects can be expected to occur within 20 to 60 min.[21-25] SCM achieves maximum plasma concentration in 17 min after a 5-mg dose,[26] and clinical effects start to be seen in 15 min.[27] FST can provide peak plasma concentrations within 30 to 40 min after consumption of a 100-μg tablet,[28] but the onset of analgesia, after fentanyl plasma levels are detectable, is affected by a much shorter delay,[12] allowing analgesia to occur in approximately 15 min. It is therefore reasonable to ask whether FST can be clinically noninferior to SCM.

This study was a double-blind, double-dummy RCT to test the noninferiority of 100 μg FST versus 5 mg SCM in the first 30 min postadministration for the treatment of severe pain episodes in a population of patients with cancer whose pain was treated with around-the-clock opioids.

METHODS

Study Design

A double-blind, double-dummy, parallel-group, noninferiority RCT was carried out at the outpatient palliative care clinic of the Fondazione IRCCS Istituto Nazionale dei Tumori–Milan. The protocol was registered in the EudraCT database and received institutional review board approval (INT 123/13).

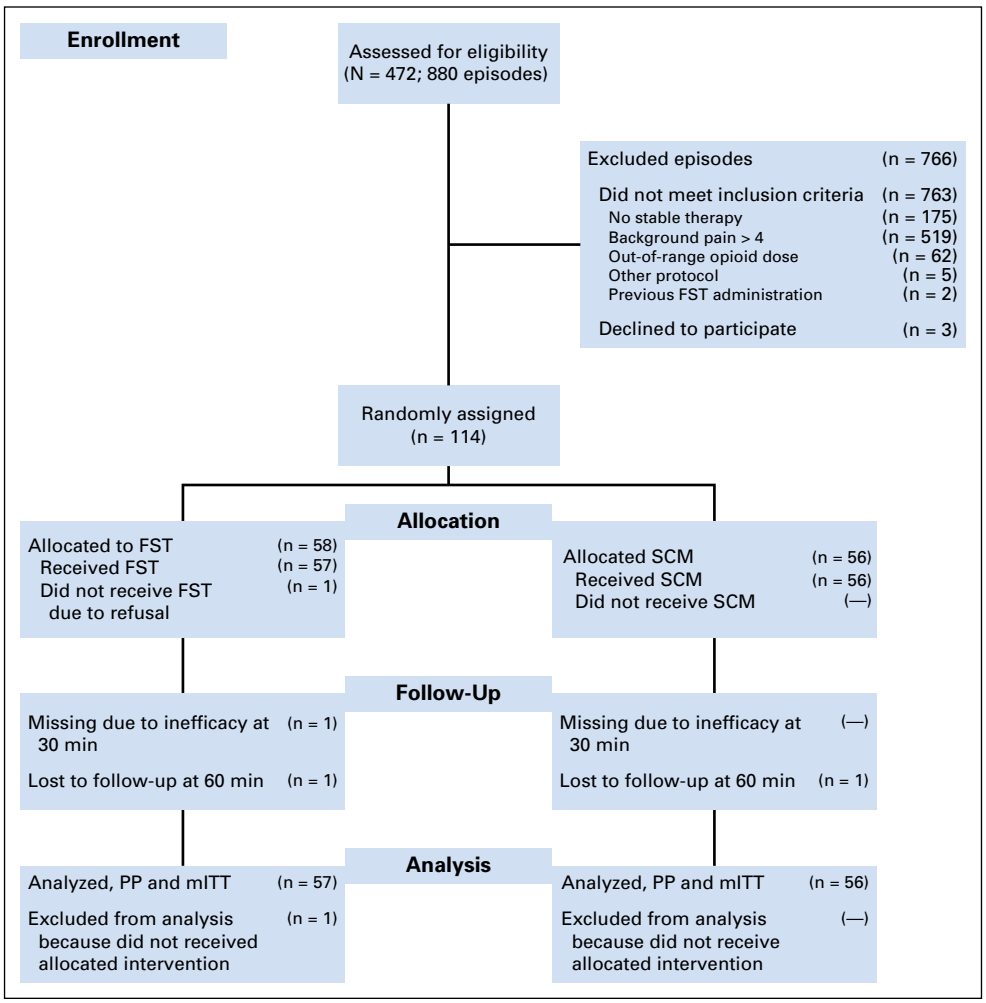

Fig 1. CONSORT flow diagram of study participants by treatment group. FST, fentanyl sublingual tablets; mITT, modified intention to treat; PP, per protocol; SCM, subcutaneous morphine.

Study Population

Outpatients who reported a severe pain episode at the time of the visit were eligible for the study if they fulfilled the following criteria: pain due to advanced cancer; current pain ≥ 6 on a 0 to 10 numerical rating scale (NRS); average PI score ≤ 4 of 10 in the previous 24 hours; stable opioid treatment in the previous 3 days; daily opioid consumption within a range of 20 to 120 mg oral morphine equivalent daily dose (OMEDD).[1] Main exclusion criteria were cognitive failure, previous therapy with TFs, and severe hepatic and/or renal impairment. Patients could participate in the trial only once. All patients enrolled provided written informed consent.

Study Procedures, Randomization, and Masking

Patients were screened for eligibility by a physician who also performed data collection. They were stratified into two groups according to their daily opioid dose assumption (OMEDD = 20-60 mg *v* 60-120 mg) and then were randomly assigned to receive either FST plus placebo or SCM plus placebo with a 1:1 allocation ratio. Randomization sequence was created using Nquery Advisor 6.0 software (Statsols, Cork, Ireland), using random block sizes of four. Sequentially numbered, opaque, sealed envelopes were used to blind the sequence to all those involved in the study. Envelopes were handled by the nurse who prepared the drugs. This nurse was not blinded to treatment allocation and did not communicate with either the patients or the physician screening and assessing them. This nurse delivered the appropriate drug kit (FST plus placebo or SCM plus placebo) to a second nurse who administered the drug. Then the physician performed subsequent assessments. Treatment allocation was blinded to all those dealing with patients, the data analyst, and other investigators, and was unveiled only at the end of data analysis.

Table 1. Baseline Clinical Characteristics of the Study Sample (N = 113)

Characteristic	FST n = 57 No. (%)	SCM n = 56 No. (%)
Age, years		
Mean (SD)	57.7 (14.4)	62.3 (9.7)
Range	23-88	39-83
Gender		
Male	26 (45.6)	29 (51.8)
Female	31 (54.4)	27 (48.2)
Primary cancer site or type		
GI tract*	8 (14.0)	7 (12.5)
Urogenital system†	13 (22.8)	3 (5.4)
Breast	9 (15.8)	13 (23.3)
Lung	9 (15.8)	10 (17.9)
Sarcoma	3 (5.3)	6 (10.7)
Head and neck	7 (12.3)	4 (7.1)
Melanoma	4 (7.0)	7 (12.5)
Other	4 (7.0)	6 (10.6)
Extent of disease		
Metastatic	51 (89.5)	51 (90.1)
Locally advanced	25 (43.9)	17 (30.9)
Karnofsky performance status		
60	2 (3.5)	4 (7.1)
70	15 (26.3)	14 (25.0)
80	25 (43.9)	26 (46.5)
90	15 (26.3)	12 (21.4)

Abbreviations: FST, fentanyl sublingual tablets; SCM, subcutaneous morphine; SD, standard deviation.
*Digestive tract, liver, pancreas.
†Ovary, prostate, kidney, uterus, bladder, vulva.

Assessment

The Italian version of the Brief Pain Inventory[29] was used to assess PI right now and on average in the previous 24 hours on a 0-to-10 NRS, where 0 indicated no pain and 10 indicated the worst pain imaginable. Pain right now was assessed once at enrollment, again immediately before study drug administration, and thereafter at 10, 20, 30, and 60 min after therapy. Typical opioid-associated adverse events (AEs; somnolence, difficulty concentrating, nausea, vomiting, dry mouth, confusion, muscle spasms, stomachache, difficulty urinating, dyspnea, and itching) were assessed at 30 and 60 min on a four-point verbal rating scale (No, A Little, Much, and Very Much) using a subset of items from the Therapy Impact Questionnaire.[30] At 30 min, patients also evaluated pain relief on a five-point verbal scale (None, Slight, Moderate, Lots, and Complete).[31] At 60 min, adverse cutaneous reactions were checked and reported, and patients were asked about preference for drug administration route.

Treatments

All study participants were administered a sublingual disintegrating tablet (fentanyl 100 μg or placebo) and a subcutaneous injection (morphine 5 mg or placebo). The 5-mg SCM dose for the control group was chosen considering that previous opioid exposure could be < 60 mg OMEDD. The suggested opioid prn dose, according to guidelines and clinical practice,[1] is

Table 2. Baseline Pain Characteristics and Analgesic Therapy (N = 113)

Characteristic and Analgesic Therapy	FST n = 57 No. (%)	SCM n = 56 No. (%)
Anatomic pain site		
Head and neck	6 (10.5)	3 (5.4)
Column	13 (22.8)	11 (19.6)
Upper limb	2 (3.5)	2 (3.6)
Lower limb	4 (7.0)	6 (10.7)
Thorax	7 (12.3)	4 (7.1)
Abdomen	4 (7.0)	7 (12.5)
Other	6 (10.5)	5 (8.9)
More than one site	15 (26.3)	18 (32.1)
Pain type*		
Somatic	49 (86.0)	43 (76.8)
Visceral	11 (19.3)	10 (17.8)
Neuropathic	27 (47.4)	24 (42.8)
Around-the clock analgesic medication in the previous 24 hours		
Codeine	13 (22.8)	11 (19.6)
Tramadol	3 (5.3)	6 (10.7)
Morphine	3 (5.3)	4 (7.1)
Oxycodone	25 (43.9)	19 (33.9)
Hydromorphone	0 (0.0)	1 (1.8)
Fentanyl	9 (15.8)	11 (19.6)
Tapentadol	4 (7.0)	4 (7.1)
As-needed medication assumed in the previous 24 hours		
Yes	8 (14.0)	4 (7.2)
No	49 (86.0)	52 (92.8)
Previous 24-hour total OMEDD, mg		
Mean (SD)	54.6 (32.1)	54.3 (34.9)
Stratum		
Low dosage (20 to 60 OMEDD)	40 (70.2)	40 (71.4)
High dosage (60 to 120 OMEDD)	17 (29.8)	16 (28.6)
Adjuvant analgesic drugs*		
Steroids	23 (40.3)	21 (37.5)
Anticonvulsants	14 (24.6)	10 (17.9)
Other	7 (12.3)	7 (12.5)

Abbreviations: FST, fentanyl sublingual tablets; OMEDD, oral morphine equivalent daily dose; SCM, subcutaneous morphine.
*Multiple responses were possible.

Table 3. Pain Intensity and Need for a Second Administration During 60 min Follow-Up, Per-Protocol Analysis

Pain Intensity*	FST	SCM	SCM-FST†
Average of pretreatment pain intensity scores	N = 57, 7.5 (1.5)	N = 56, 7.5 (1.4)	
Pain intensity score at 10 min	N = 57, 5.9 (1.8)	N = 56, 5.4 (2.0)	
Pain intensity score at 20 min	N = 57, 5.0 (2.3)	N = 56, 4.4 (2.2)	
Pain intensity score at 30 min	N = 56, 3.9 (2.5)	N = 56, 3.6 (2.4)	
Average follow-up pain intensity scores 0 to 30 min (AVP_30)*	N = 57, 5.0 (2.1)	N = 56, 4.5 (2.0)	−0.49‡ (−1.1 to 0.09)
Administration of a second dose at 30 min	N = 57, 50.9%	N = 56, 37.5%	−13.4%‡ (−30% to 3%)
Pain intensity score at 60 min	N = 55, 2.9 (2.25)	N = 55, 2.6 (1.9)	−0.36‡ (−1.0 to 0.3)

NOTE. Results for FST and SCM are shown as No., mean (SD). Results for SCM-FST are shown as between-group mean difference (95% CI).
Abbreviations: FST, fentanyl sublingual tablets; SCM, subcutaneous morphine.
*Pain intensity right now (0-10 numerical rating system).
†Two-sided CI.
‡Adjusted by baseline pain intensity.

20% of the total daily dose, and in the case of 60 mg OMEDD, this would account for a 4-mg SCM prn dose (= 12 mg oral dose). The study conditions were therefore balancing the risk of overdosing (patients with < 60 mg OMEDD) and underdosing (patients with 60-120 mg OMEDD). The dose of 100 μg FST was chosen on the basis of data showing it was equianalgesic to the 4.5-mg dose of intravenous morphine in a humane experimental pain model[32] and because it is the initial dose recommended by the registered prescription requirements. Placebo was 1 mL of saline solution or a sublingual tablet exactly reproducing the fentanyl preparation. Remedication was possible after 30 min for patients who reported pain reduction of less than two points or pain relief less than or equal to moderate.

End Point Definition, Noninferiority Margin, and Sample Size Calculation

The average of pain right now scores at 10, 20, and 30 min (AVP_30) was identified as the main outcome measure. Analysis of covariance (ANCOVA) of AVP_30 adjusted by the average of pretreatment scores was the main analysis.[33-35] For sample size calculation, the formula proposed by Frison and Pocock[33] was applied and adapted for noninferiority trials as suggested by Julious et al.[36] The noninferiority margin (NIm) was set at one third of the minimum clinically important difference (MCID).[36] Because two points difference in PI on a 0 to 10 NRS is considered the MCID in cancer pain,[37,38] NIm was defined as 0.6. Data from the medical charts of 16 patients previously treated with SCM (eight patients) and FST (eight patients) for BTP were used to estimate sample size calculation parameters (outcome variability and correlation). A sample size of 56 patients in each of the two arms was calculated to guarantee a power of 90% to reject the inferiority null hypothesis, with a one-sided 97.5% CI (α = 0.025), assuming that variability of the AVP_30 was 1.0 and 2.4 in the FST and SCM arms, respectively, and that the correlations between repeated measurements were 0.7 and 0.65 among the pretreatment and post-treatment score sets, respectively; correlation between pretreatment and post-treatment scores was set at 0.6. The conservative choice of a nominal α of 0.025 was aimed at further limiting the chance of erroneously declaring FST noninferior to SCM. Secondary end points were analgesic efficacy at 60 min, proportion of patients needing a second dose of opioid, proportion of patients who expressed a preference for each of the two administration routes, AEs, and serious AEs.

Statistical Analysis

Primary end point noninferiority analysis was carried on the per-protocol (PP) population and repeated, for sensitivity reasons, on the modified intention-to-treat (mITT) population. All other secondary end points were tested for superiority of FST to SCM, and the analyses were carried out on the mITT population. The two-sided 95% CI for the between-treatment difference (SCM-FST) in the main end point (AVP_30) was calculated using ANCOVA, with average of pretreatment PI scores as the covariate. Because the lower bound of a two-sided 95% CI is equivalent to the lower bound of a one-sided 97.5% CI, according to CONSORT recommendations,[39] results were reported in terms of two-sided CIs, which provide additional information with respect to the corresponding one-sided CIs. The criterion for declaring FST noninferior to SCM was a lower bound of the two-sided 95% CI above the NIm of −0.6 (the negative sign is due to the direction of the group difference definition). An ANCOVA model adjusted also for previous 24-hour opioid OMEDD was

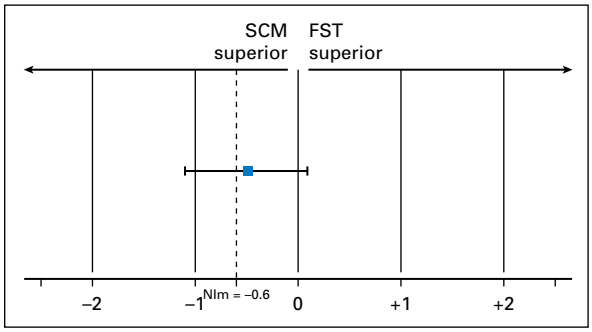

Fig 2. The 95% CI and noninferiority margin of the between-group difference in the main end point, that is, the average of pain scores in the first 30 min post-treatment. FST, fentanyl sublingual tablets; NIm, noninferiority margin; SCM, subcutaneous morphine.

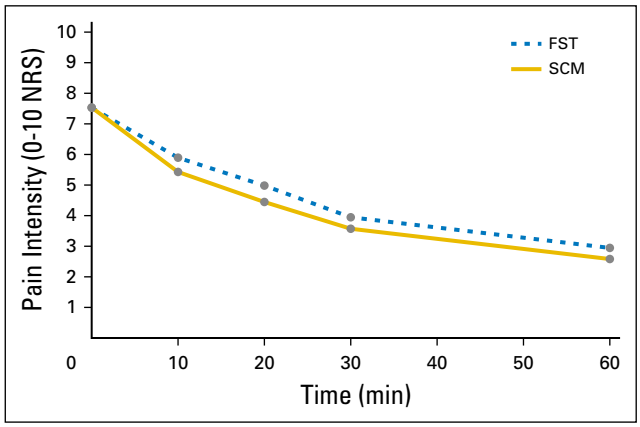

Fig 3. Profile of pain reduction in the first 60 min post-treatment by study drug. FST, fentanyl sublingual tablets; NRS, numerical rating scale; SCM, subcutaneous morphine.

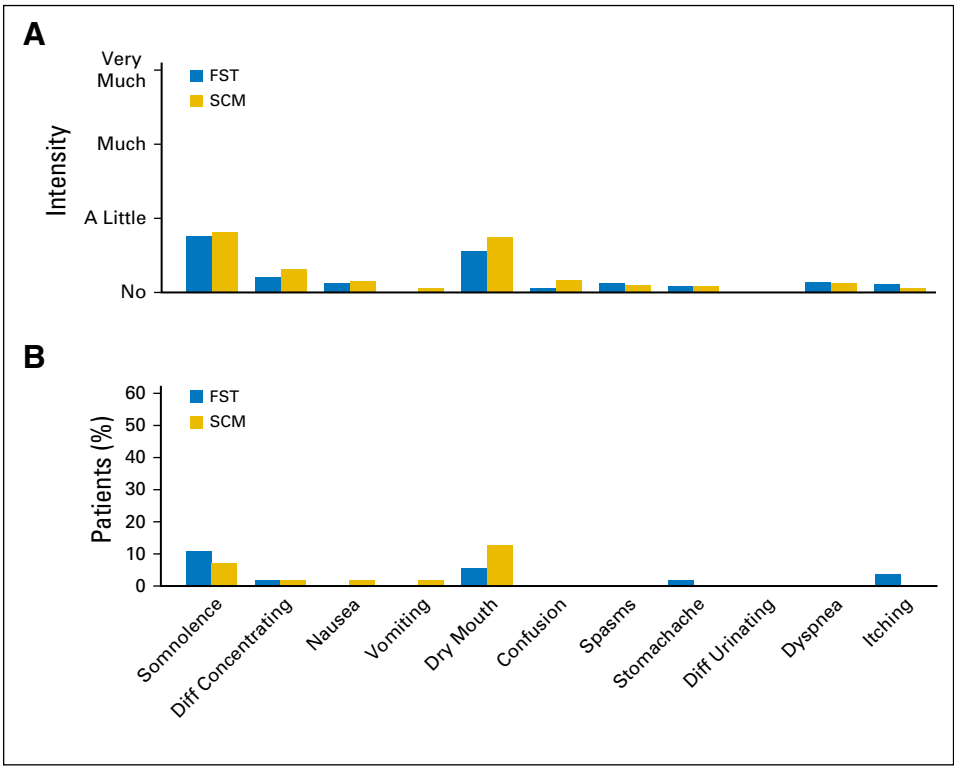

Fig 4. Adverse event profile during follow-up by study drug: (A) the average of follow-up scores for each adverse event; (B) the percentage of patients scoring Much or Very Much at either 30 or 60 min. Diff, difficulty in; FST, fentanyl sublingual tablets; SCM, subcutaneous morphine.

estimated. More detail on mITT and PP population definitions, as well as on statistical analyses for secondary outcomes, are reported in the Appendix (online only).

RESULTS

From December 2013 to August 2015, 472 outpatients with a severe pain episode were screened for eligibility. Patients not previously included in the study could be screened more than once (76 patients were screened three times or more; Fig 1). The main reason for ineligibility was previous 24-hour uncontrolled background pain. A total of 114 eligible patients were randomly assigned to FST (n = 58) or SCM (n = 56). One patient (FST group) withdrew consent before drug administration and was excluded from the analysis. All patients completed PI and AE assessments, but one patient withdrew before evaluation at 30 min due to inefficacy (FST group) and two patients (one in each group) were lost to follow-up before evaluation at 60 min (Fig 1). None of these were considered major protocol violations, and the patients were included in both the PP and mITT populations. Consequently, PP and mITT populations were the same.

The distribution of baseline clinical, demographic, and pain-related characteristics of enrolled patients was similar in the two treatment groups except for some minor imbalance in cancer site (Table 1) and in around-the-clock and prn medications in the previous 24 hours (Table 2). Exploratory comparison of arms on baseline characteristics did not yield any statistically significant result.

Table 3 lists PI data at different time points. Pretreatment mean PI was 7.5 in both groups. Mean AVP_30 was 5.0 and 4.5, respectively, for FST and SCM, with a between-group difference of −0.49 and a 95% CI of −1.10 to 0.09, which includes NIm (Table 3; Fig 2). Descriptive responder analyses at 30 min posttreatment indicated that a PI reduction of 33% was achieved in 71% of patients with both treatments, whereas a 50% reduction was more frequent with SCM (57%) than with FST (52%; data not shown in table). Main end point results adjusted by previous 24-hour opioid OMEDD were superimposable on unadjusted ones (between-group difference on AVP_30, −0.49; 95% CI, −1.10 to 0.09).

Between-group difference at 60 min was slightly reduced (−0.36; 95% CI, −1.0 to 0.3), but the 95% estimate still did not indicate superiority of one of the two drugs over the other. Figure 3 shows the profile of pain reduction in the first 60 min posttreatment and indicates that the mean difference in efficacy between FST and SCM was consistently in between 0.3 and 0.5 at all time points. Patients taking FST more frequently received a second analgesic drug dose after 30 min (51% *v* 37%; risk difference, −13%; Table 3).

Moderate nausea was spontaneously reported by one patient (FST group), and it was judged possibly related to the study drug. One patient had a moderate skin reaction with SCM. No patients reported serious AEs. Figure 4 shows the distribution of the detailed AE profile during follow-up. Symptom mean intensity scores of follow-up assessments were always lower than A Little (Fig 4A), and patients scoring Much or Very Much at either 30 or 60 min were no more than 13% with both treatments (Fig 4B). None of the *t* tests comparing the two treatment on follow-up intensity scores of each AE had significant results (data not reported). Sublingual route of administration was preferred by 93% of patients (95% CI, 86% to 97%), with a slight difference by treatment (91% in FST and 95% in SCM).

DISCUSSION

To our knowledge, this is the first trial comparing FST with SCM for the treatment of severe cancer pain episodes. The results did not show the noninferiority of FST 100 μg compared with SCM 5 mg, with a two-sided 95% CI lower bound of the group difference in AVP_30 reaching −1.1 (Table 3), which is below the predefined NIm of −0.6 (Fig 2). The NIm was carefully chosen to be small and potentially of limited clinical significance by using one third of two points, that is, the MCID in PI, according to empirical data.[37,38] The profile of the analgesic effect (Fig 3) showed that with both treatments, pain quickly decreased from mean scores of 7.5 at baseline to scores below four at 30 min, with SCM showing a slightly better efficacy. In addition, responder analysis at 30 min showed a moderate advantage of SCM over FST (57% *v* 52%, respectively, reported a pain reduction of at least 50% of the baseline pain, but no difference was found with a 33% PI reduction). Consistently, the trend of remedication after 30 min was in favor of SCM, although the difference was not statistically significant (Table 3).

Available evidence comparing TFs with other prn opioid medications used in clinical practice, such as oral and parenteral morphine, is limited[15-18] and the strength not sufficient[40] to change clinical guidelines.[41] Therefore, the comparison of FST with oral morphine demands more research. However, our results can help to clarify another clinically relevant research question, which is how FST compares with SCM, and informs clinical practice.

Both treatments in our study were safe and well tolerated (Fig 4). This study also confirmed that patients with an exposure to opioids < 60 mg OMEDD can benefit from 100 μg FST or 5 mg SCM without harm. Patient preference was strikingly in favor of the sublingual route (93%). These results support the rationale for a noninferiority trial design, making a small difference in pain relief acceptable, while considering the evident difference in invasiveness, as confirmed by patients' preference and the obvious ease of administration in all care settings implied by the sublingual route.

Presently, FST tablets are indicated for patients with cancer pain already tolerant to a moderate dose of systemic opioids (OMEDD ≥ 60 mg). This may be a use limitation in patients with lower opioid exposure and severe pain episodes. In this study, we extended the use of FST to patients treated with lower opioid dosage (80 patients [71%] receiving an OMEDD < 60 mg; Table 2). Recent evidence[18] suggests that differences in previous exposure to opioids can affect efficacy of the prn dose. For these reasons, we stratified the study population by previous opioid exposure to avoid imbalance between treatment groups on this potentially relevant variable. A secondary analysis adjusting for previous opioid exposure showed identical estimates of the main end point, thus suggesting no effect of opioid exposure on the relative efficacy between FST and SCM at the doses used in this study.

The relative potency between FST and SCM is unknown, but fentanyl and morphine show a relative potency ratio of 1:100 after intravenous administration.[42] The ratio of 1:50 for FST versus SCM was chosen in this trial on the basis of the ratio 1:45 found in a study comparing FST with intravenous morphine in healthy human volunteers, which also allowed wide CIs.[32] A larger intraindividual variation in bioavailability of FST versus SCM can also be expected, and the combination of these factors is consistent with a less reliable analgesic effect across individual patients and a more frequent need for titration of the dose with FST than with SCM. Available comparative data suggest titrating the dose of FST starting at 100 μg regardless of previous opioid exposure,[41] but, as mentioned earlier, recent evidence suggests using an initial SBF dose that is proportional to opioid exposure.[18] Future studies should therefore address the optimal mode of dose finding for FST.

Study limitations include the lack of a placebo control group. However, this option could be viewed as nonethical, considering that FST was already compared with placebo and that morphine is considered a standard treatment for intense cancer pain episodes.[1]

In conclusion, this trial did not show noninferiority of 100 μg FST versus 5 mg SCM for the treatment of intense pain episodes but provides a reliable estimate of the relative efficacy of the two interventions. Both treatments were well tolerated, and patients preferred the sublingual route of administration. FST can be a safe alternative to treat severe cancer pain episodes, including for patients with opioid exposure of < 60 mg OMEDD, and it can be more appropriate than SCM in some settings of care for practical reasons, but it cannot be generally recommended as a substitute for SCM.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at ascopubs.org/journal/jco.

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Fentanyl Sublingual Tablets Versus Subcutaneous Morphine for the Management of Severe Cancer Pain Episodes in Patients Receiving Opioid Treatment: A Double-Blind, Randomized, Noninferiority Trial

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Appendix

Univariable exploratory comparison of arms on baseline characteristics was performed with Fisher's exact test and independent samples *t* test for categorical and continuous variables, respectively. Modified intention-to-treat population was composed of all participants as originally allocated after randomly assigned, who provided at least one post-treatment assessment; per-protocol population was defined as a subset of the modified intention-to-treat population who completed the study without any major protocol violations.

For descriptive purposes, the number of patients reporting a percentage of pain reduction at 30 min of at least 33%[37] and of at least 50% (McQuay H, Moore A: An Evidence-Based Resource for Pain Relief. Oxford, United Kingdom, Oxford University Press, 1998) was also calculated. Analysis of covariance adjusted for baseline was also used for estimating the between-treatment difference in analgesic efficacy at 60 min. The between-treatment risk difference of remedication at 30 min was estimated through logistic regression. We used the *t* test to compare the two treatments on the average of post-treatment adverse effect intensity scores. The percentage of patients scoring adverse events as "Much" or "Very Much" at either 30 or 60 min was also calculated for descriptive purposes.