*Original Article*

# An Open-Label Extension Study to Investigate the Long-Term Safety and Tolerability of THC/CBD Oromucosal Spray and Oromucosal THC Spray in Patients With Terminal Cancer-Related Pain Refractory to Strong Opioid Analgesics

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## Abstract

**Context.** Chronic pain in patients with advanced cancer poses a serious clinical challenge. The Δ9-tetrahydrocannabinol (THC)/cannabidiol (CBD) oromucosal spray (U.S. Adopted Name, nabiximols; Sativex®) is a novel cannabinoid formulation currently undergoing investigation as an adjuvant therapy for this treatment group.

**Objectives.** This follow-up study investigated the long-term safety and tolerability of THC/CBD spray and THC spray in relieving pain in patients with advanced cancer.

**Methods.** In total, 43 patients with cancer-related pain experiencing inadequate analgesia despite chronic opioid dosing, who had participated in a previous three-arm (THC/CBD spray, THC spray, or placebo), two-week parent randomized controlled trial, entered this open-label, multicenter, follow-up study. Patients self-titrated THC/CBD spray ($n = 39$) or THC spray ($n = 4$) to symptom relief or maximum dose and were regularly reviewed for safety, tolerability, and evidence of clinical benefit.

**Results.** The efficacy end point of change from baseline in mean Brief Pain Inventory-Short Form scores for "pain severity" and "worst pain" domains showed a decrease (i.e., improvement) at each visit in the THC/CBD spray patients. Similarly, the European Organization for Research and Treatment of Cancer

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Quality of Life Questionnaire-C30 scores showed a decrease (i.e., improvement) from baseline in the domains of insomnia, pain, and fatigue. No new safety concerns associated with the extended use of THC/CBD spray arose from this study.

**Conclusion.** This study showed that the long-term use of THC/CBD spray was generally well tolerated, with no evidence of a loss of effect for the relief of cancer-related pain with long-term use. Furthermore, patients who kept using the study medication did not seek to increase their dose of this or other pain-relieving medication over time, suggesting that the adjuvant use of cannabinoids in cancer-related pain could provide useful benefit. J Pain Symptom Manage 2013;46:207−218. 

***Key Words***
*Cancer, cannabinoid, delta-9-tetrahydrocannabinol, pain, THC/CBD oromucosal spray*

## *Introduction*

Chronic unremitting pain that results from cancer adversely affects a large portion of the population of cancer patients. Worldwide, more than 10 million people are diagnosed with cancer each year, and it has been estimated that, by 2020, this figure will increase to more than 15 million people a year.[1] The prevalence of cancer-related pain directly correlates with the stage of disease, with more than 70% of patients in the advanced stages of cancer reporting pain.[2,3]

Currently, opioids are the principal agents used in the management of cancer-related pain, but the therapeutic benefit of their prolonged use is frequently offset by the development of undesirable side effects.[4] Although opioids are the standard choice for the treatment of cancer patients with moderate-to-severe pain, adjuvant therapy is recommended by both the World Health Organization guidelines[5] and the Agency for Health Care Policy and Research guidelines.[6]

Cannabinoids (CBs) have been identified as potential adjuvant analgesics and are currently under investigation. It is now generally accepted that there are at least two types of CB receptor, $CB_1$ and $CB_2$, both members of the superfamily of G protein-coupled receptors.[7] However, CBs also may demonstrate activity at other receptors, including G protein-coupled receptor 55,[8] transient receptor potential vanilloid-1,[9] and adenosine receptors.[10] $CB_1$ receptors are predominantly located in the central nervous system, whereas $CB_2$ receptors are primarily expressed in the periphery by immune cells. These receptors are targeted by the agonists that are produced in mammalian tissues, and this system of receptors and endocannabinoids together constitute the endocannabinoid system.

The cannabis plant contains more than 60 CBs. The CB extracts Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are two potentially therapeutic components in *Cannabis sativa L.*,[11] and both have shown promise in relieving cancer-related pain.[12,13] The principal pharmacologic effects of THC include analgesic, muscle relaxant, antiemetic, appetite stimulant, and psychoactive effects;[14] CBD has been described to have anticonvulsant, muscle relaxant, anxiolytic, neuroprotective, antioxidant, and antipsychotic activity, and also has been shown to reduce the anxiety and psychoactive effects of THC.[11,15]

In animal studies, CBs and opioids have synergistic effects in both chronic and acute pain models,[16−19] although the mechanisms underlying these effects remain unclear.[16] In a recent clinical study, patients with chronic pain who received a combination of vaporized cannabis and opioid (morphine or oxycodone) reported a significant reduction in pain after the addition of cannabis, demonstrating an augmentation of the analgesic effects of opioids with cannabis.[20] These studies suggest that the adjuvant use of CBs with opioids may benefit patients with cancer-related pain.

The endocannabinoid system modulator THC/CBD spray (U.S. Adopted Name,

nabiximols; trade name, Sativex® [GW Pharmaceuticals, Wiltshire, UK]; note that Sativex does not have an international nonproprietary name) is formulated from the plant-based extracts prepared from genetically distinct chemotypes of *Cannabis sativa L.* developed to contain high and reproducible yields of THC and CBD in an approximately 1:1 ratio. Prepared in a solution containing ethanol, propylene glycol, and peppermint oil flavoring, it is delivered as an oromucosal spray. THC/CBD oromucosal spray has been shown to have analgesic efficacy in peripheral neuropathic pain[21] and multiple sclerosis-induced pain and spasticity.[22–24] Moreover, the parent study to the current investigation evaluated the efficacy of THC/CBD spray and THC spray in patients with cancer-related pain in a randomized controlled trial (RCT) setting and found THC/CBD spray to be an efficacious treatment for the relief of intractable pain in patients with advanced disease who experienced inadequate analgesia despite chronic opioid treatment.[25] The primary analysis for the parent RCT was the change from baseline in mean pain 0–10 numerical rating scale (NRS) score at the end of two weeks of double-blind treatment with THC/CBD spray, THC spray alone, or placebo. The change in NRS score was statistically significant in favor of THC/CBD spray compared with placebo at the end of treatment, with a reduction of 0.67 points ($P = 0.014$) in pain score. Additionally, twice as many patients in the THC/CBD spray group compared with those in the placebo group demonstrated a 30% or greater reduction in pain NRS score at the end of treatment. The odds ratio for comparison of responders between THC/CBD spray and placebo treatment groups was 2.81 (95% CI 1.22–6.50; $P = 0.006$). No significant changes were observed in the THC-alone treatment group.[25]

Although the efficacy of THC/CBD spray has been demonstrated in the setting of RCTs, the long-term effects of cannabis use in patients with cancer-related pain has not previously been established, and very few data exist regarding tolerance. To address the need for more information, this follow-up study was conducted to collect safety and tolerability data for long-term exposure to THC/CBD spray and THC spray.

## Methods

### Design

Patients who had previously participated in a two-week parent RCT to investigate the efficacy, safety, and tolerability of THC/CBD spray and THC spray in patients with cancer-related pain[25] were invited to take part in this long-term, open-label, follow-up study, which took place in 22 study sites, including 21 centers in the U.K. and one in Belgium. Those who took part in the parent RCT in Romania were not invited to take part in the extension study. There was staggered entry into the extension study as patients completed the parent RCT. As such, there were diminishing numbers of patients providing data over time, which was, in general, not the result of patient withdrawal. The study was approved by the relevant Institutional Review Boards or Ethical Committees in both countries and was conducted in accordance with the principles of the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice.

To assess the safety and tolerability of long-term therapy with THC/CBD spray, visits occurred at the withdrawal visit of the parent RCT or at extension study screening, 7–10 days later, then every four weeks, and at study completion or withdrawal. At each visit, the following information was recorded: adverse events (AEs), vital signs, blood sample analyses data, pain control assessment, and any changes in current medical conditions and current dose of study medication.

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) and Brief Pain Inventory Short-Form (BPI-SF) also were completed. Continuation within the study was conditional on satisfactory reports of tolerability, efficacy, and dosing regimen. Both THC/CBD spray and THC-only spray were used, aiming to ascertain if the inclusion of CBD provided a different efficacy or safety profile.

### Inclusion and Exclusion Criteria

*Study Entry Inclusion Criteria.* Only patients who had taken part in, fully complied with the study requirements of, and had not experienced an unacceptable AE (in the opinion of the investigator) in the parent RCT[25] were

eligible for the present study, as long as they were expected to receive clinical benefit from THC/CBD spray with acceptable tolerability (in the opinion of the investigator). Inclusion in the extension study was irrespective of previous treatment allocation in the parent RCT.

*Exclusion Criteria.* Patients with a history of severe cardiovascular, renal, hepatic, convulsive, or psychiatric disorder other than the depression associated with their pain or underlying illness were excluded from study participation as were patients currently taking levodopa. Patients who were pregnant, lactating, or not using adequate contraception also were excluded, as were patients with oral cavity cancers or whose previous treatments had included radiotherapy to the floor of the mouth.

### *Treatment Groups and Doses*

A pump action oromucosal spray was used to deliver the study medication. Each 100 μL actuation of THC/CBD spray delivered 2.7 mg of THC and 2.5 mg of CBD to the oral mucosa. Each actuation of THC delivered 2.7 mg of THC, and each actuation of placebo (in the parent RCT) delivered the excipients plus colorants. Patients self-administered the medication to their optimal dose. At the first study visit, the initial dosing was supervised by the investigator. Detailed instructions for the initial days of titration were provided for individuals based on the investigators' assessment of how well they had tolerated the medication during the introductory doses. Thereafter, written instructions on dose titration were provided, and patients were advised how to self-titrate to either symptom relief or maximum tolerated dose, with a restriction of eight actuations in a three-hour period up to a maximum of 48 sprays per 24-hour period. Dose increases also were limited to a maximum of 50% of the previous day's dose, and patients established a dosing regimen over seven to 10 days until the second extension study visit. Most patients initially received THC/CBD spray but could be switched to THC spray if both the investigator and the patient felt that optimal pain control was not reached and/or the patient was experiencing unacceptable AEs. Investigators were blinded to the previous treatment allocation in the parent RCT.

### *Study End Points*

*Efficacy End Points.* The efficacy end points for this study were recorded in the patient diaries, as well as BPI-SF and EORTC QLQ-C30 scores. On each occasion of completing the BPI-SF, patients were asked to rate, on a scale of 0−10, the severity of their pain, the average and worst pain, and the amount that pain interfered with their daily life. For each of these parameters, a decrease in score represented an improvement. On each occasion of completing the EORTC QLQ-C30, patients were asked to rate 14 domains on a scale of 0−100. Six domains concerned functional status, in which an increase in the score represented an improvement. The domains included global health status, physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning. Eight domains concerned adverse symptoms, in which a decrease in the score represented an improvement. These domains were fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, and diarrhea. A final domain concerned financial difficulties.

A recent study in breast cancer patients with bone metastasis estimated the minimally important difference (MID) in worst pain BPI-SF scores to be two points.[26] Another recent study in lung cancer patients estimated the MID in EORTC QLQ-C30 scores for deteriorating patients in the different questionnaire domains. Their estimates of the MID in points were physical (4, 6); role (5, 5); social (7, 9); global health status (4, 4); fatigue (6, 11); and pain (3, 7).[27]

*Safety End Points.* The safety end points of this study included the incidence of nonelicited AEs, laboratory parameters pretreatment and post-treatment, and use of rescue medication and maintenance analgesic medication.

### *Statistical Methods*

As this was a noncomparative study, no formal hypothesis testing was performed. The statistics, therefore, are descriptive. All patients who took at least one dose of study medication after the date of the first visit, and yielded on-treatment efficacy data, were classed as the efficacy and safety population. For the efficacy parameters BPI-SF and EORTC QLQ-C30,

summaries were provided only for time points where nine or more patients contributed data. Changes from the baseline that were established in the initial randomized study[25] were used in this extension study because the patients would be a mixture of THC/CBD spray, THC spray, and placebo-treated patients at the onset of the extension study. Changes from this baseline would not be a representation of any coherent population. The parent RCT baseline, however, does represent the patients' status as they were before the start of the randomized trial.

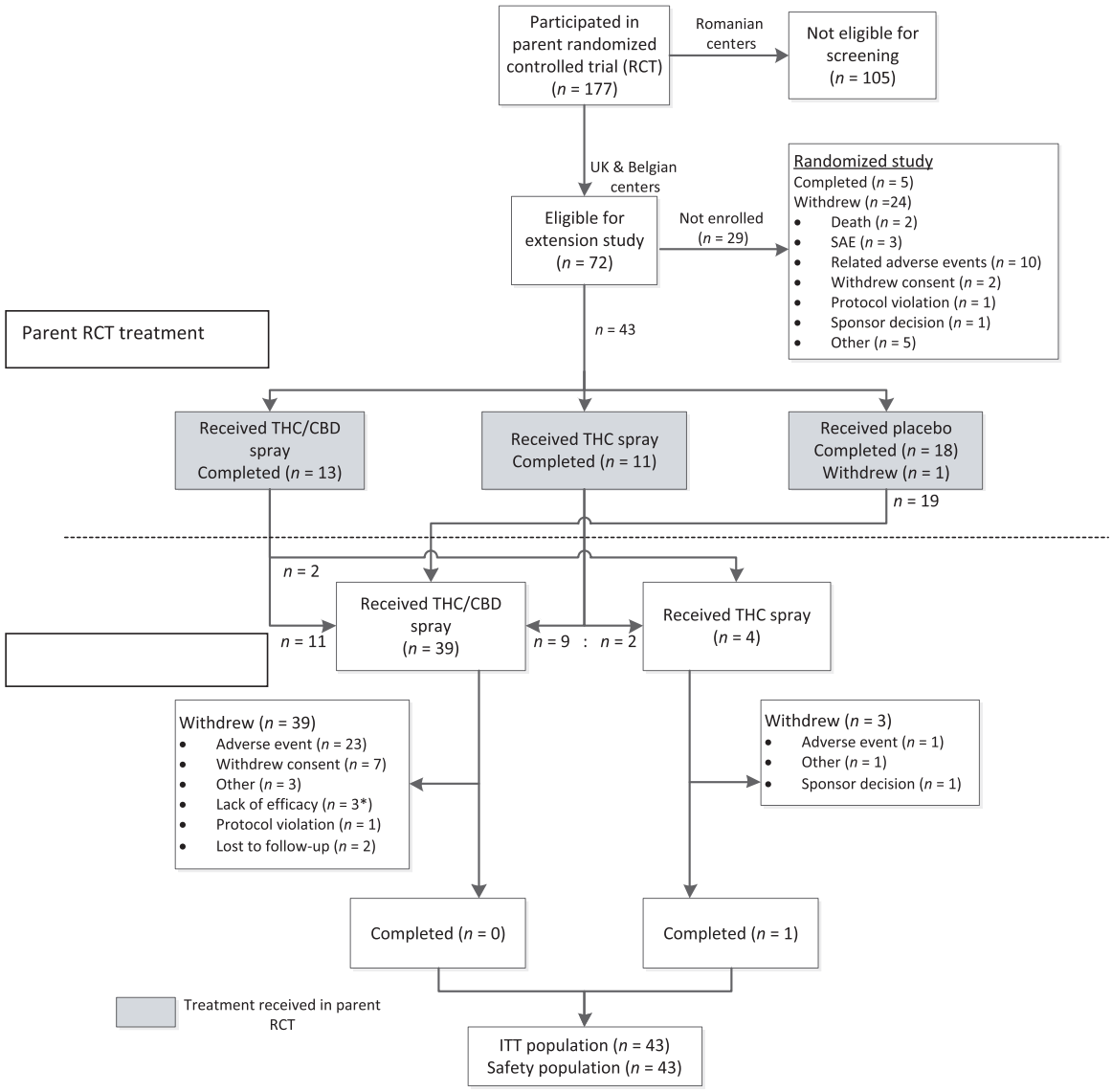
*Sample Size.* There was no formal sample size for this study.

## Results

Of the 177 patients who participated in the parent RCT,[25] 48 were eligible for the extension study. Of these, 43 patients were enrolled and analyzed from 23 study sites in the U.K. and Belgium (13 patients had received THC/CBD spray, 11 had received THC spray, and 19 had received placebo). One patient was still on the medication at the completion of the study whereas 42 patients were not. A summary of the breakdown of patients enrolled in this study is shown in Fig. 1. The mean ± SD duration of cancer in these patients was 2.8 ± 1.88, 4.8 ± 5.07, and 7 ± 7.5 years for THC/CBD spray, THC spray, and placebo treatment groups, respectively, at the parent RCT baseline.[25] The overall mean duration of cancer was 5.2 years with a median of 3.7 years. The maximum duration of diagnosis was 34.1 years, and the minimum was 0.3 years. The four patients who started the extension study taking THC spray had had diagnoses of cancer for 1.0, 7.1, 5.2, and 4.7 years, respectively, when screened for the randomized study. Three patients had diagnoses of breast cancer and one had a diagnosis of myeloma. Two patients had previously been randomized to THC/CBD spray and two to THC spray. The five most commonly reported primary disease sites were breast, prostate, rectum, lung, and bone, with prevalences of 21%, 16%, 16%, 7%, and 5%, respectively. The remaining sites each contributed 2% to the total. Five of the seven patients with a prostate primary had received placebo in the randomized study, and only one of the seven patients with a rectal primary had received THC/CBD spray in the randomized study; otherwise, the distribution of sites by previous randomized therapy was not notably unbalanced. The most commonly reported pain type was mixed pain, affecting over half of all the patients, followed by neuropathic pain (37% of all patients) and bone pain (28% of patients). Thirty-three patients (77%) reported at least one current medical condition. The conditions reported most commonly affected the gastrointestinal (53%), psychiatric/psychological (30%), and the cardiovascular (26%) body systems. Disorders of the remaining body systems affected fewer than 25% of patients. Not surprisingly, this distribution was similar to the current medical and surgical conditions reported on entry to the preceding randomized study. Other study population demographics are displayed in Table 1 and Table 2. During the last seven days of dosing, patients receiving THC/CBD spray administered on average 5.4 ± 3.28 sprays per day, and patients receiving THC spray took on average 14.5 ± 16.84 sprays per day.

### *Concomitant Medication*

As would be expected in this group of patients, many were receiving concomitant medications for analgesia. Patients were allowed to vary their concomitant analgesic medication but discussed with investigators which of their current medications they could reduce or discontinue safely in the event of symptom relief. The most common nonopioid concomitant medication taken by those in the THC/CBD and THC spray groups were paracetamol (acetaminophen) taken by five (13%) and two (50%) patients, respectively. Diclofenac also was taken by three (8%) THC/CBD spray patients, with all other nonopioid concomitant medications taken by two or fewer patients in this group. In the THC spray group, one patient each also received or was receiving the bisphosphonate pamidronate disodium, ketamine, and pethidine. The most common rescue opioid medications used by the THC/CBD spray group were diamorphine and morphine sulfate, used by nine (23%) patients. Six (15%) patients in this group also received prolonged-release or immediate-release morphine. The most common rescue opioid




*One subject changed to THC alone after six days and withdrew after a further 11 days.

Fig. 1. Breakdown of patients enrolled in the study. RCT = randomized controlled trial; SAE = serious adverse event; THC = Δ9-tetrahydrocannabinol; CBD = cannabidiol; ITT = intention to treat.

medications used by the THC spray group were oxycodone used by two (50%) patients, with diamorphine, morphine sulfate, Oramorph® (Boehringer Ingelheim, Ingelheim, Germany), Oxycontin® (Napp Pharmaceuticals, Cambridge, UK), and Sevredol® (Napp Pharmaceuticals, Cambridge, UK) each taken by one (25%) patient.

*Treatment Duration*

The median duration of treatment with THC/CBD spray for the 39 patients who received it was 25 days, with a minimum of two days and a maximum of 579 days. The median duration of treatment with THC for the four patients who received it was 151.5 days, with a minimum of four days and a maximum of 657 days. Fifteen patients on THC/CBD spray received treatment for less than two weeks, five for two weeks to one month, seven from one to three months, four from three to six months, five for six months to one year, and three for one year and beyond. Of the four patients on THC spray, one received it for four days, one for almost two months (51 days), one for nine months, and one for almost two years (657 days).

*Table 1*
**Study Population Demographics**

| Category | THC/CBD Spray, *n* (%) | THC Spray, *n* (%) |
|---|---|---|
| Total[a] | 39 | 4 |
| Gender | | |
| Male | 23 (59) | 1 (25) |
| Female | 16 (41) | 3 (75) |
| Ethnic origin | | |
| White/Caucasian | 38 (97) | 4 (100) |
| Asian | 1 (3) | 0 |
| Current smoker | 9 (23) | 0 |
| Previous cannabis use | 10 (26) | 1 (25) |
| | Mean (SD) | Mean (SD) |
| Age (years) | 57.5 (13.5) | 58.6 (6.3) |
| BMI (kg/m$^2$) | 24.3 (3.7) | 25.4 (4.5) |
| Alcohol (units/week) | 3.1 (5.7) | 0.5 (1.0) |

THC = Δ9-tetrahydrocannabinol; CBD = cannabidiol.
[a]One subject took THC/CBD spray on entry to the study but began THC spray after one week and received THC spray for 11 days before withdrawing because of lack of efficacy.

### *Primary Efficacy Analysis*

For the analyzed parameters of the BPI-SF, a decrease from baseline in mean score at all time points was observed for both "pain severity" and "worst pain" scores, suggesting an improvement in pain with time (Fig. 2). However, at each visit, most investigators considered that their patients' pain control was suboptimal.

There was little discernible pattern in the mean scores from the EORTC QLQ-C30 for functional status domains except that in the domain of physical functioning, a negative change from baseline (worsening) was observed at each time point. No deleterious effect was observed in the domain of cognitive functioning, although the number of patients was small (Fig. 3).

For the EORTC QLQ-C30 domains concerning AEs, improvements over time were observed in the domains of insomnia (54.1−40.5, 26% decrease) and pain (83.3−63.1, 24% decrease) between baseline and Week 5. There also was a decrease in the mean score compared with baseline in the domain of fatigue at each analyzed visit. In contrast, a worsening at each visit was observed in the domain of nausea and vomiting (24.4−35.7, 46% increase from baseline to Week 5) (Fig. 4). As for the BPI-SF and physical functioning EORTC QLQ-C30 data sets, the number of patients contributing data to these analyses decreased with time.

*Table 2*
**Primary Cancer Sites, Pain Classifications, and Oral Morphine Equivalents (by Randomized Treatment Group in Parent RCT)**

| Category | THC/CBD Spray (*n* = 13), *n* (%) | THC Spray (*n* = 11), *n* (%) | Placebo (*n* = 19), *n* (%) |
|---|---|---|---|
| Primary cancer sites | | | |
| Breast | 3 (23) | 3 (27) | 3 (16) |
| Prostate | 1 (8) | 1 (9) | 5 (26) |
| Lung | 1 (8) | 2 (18) | 0 |
| Gastrointestinal | 3 (23) | 1 (9) | 4 (21) |
| Other | 5 (40) | 4 (36) | 7 (37) |
| Pain classification | | | |
| Neuropathic | 3 (23) | 5 (45) | 8 (42) |
| Somatic | 0 | 3 (27) | 2 (11) |
| Visceral | 2 (15) | 0 | 0 |
| Incident | 1 (8) | 0 | 2 (11) |
| Mixed | 7 (54) | 7 (64) | 11 (58) |
| Bone | 4 (31) | 1 (9) | 7 (37) |
| Maintenance and rescue opioid medications | | | |
| Drugs used in opioid dependence | | | |
| Methadone | 0 | 0 | 1 (5) |
| Natural opium alkaloids | | | |
| Diamorphine | 6 (46) | 1 (9) | 3 (16) |
| Hydromorphone | 0 | 1 (9) | 1 (5) |
| Morphine | 2 (15) | 0 | 3 (16) |
| Morphine sulfate | 4 (31) | 2 (18) | 4 (21) |
| MST® | 1 (8) | 0 | 5 (26) |
| Oramorph® | 4 (31) | 1 (9) | 2 (11) |
| Oxycodone hydrochloride | 1 (8) | 3 (27) | 1 (5) |
| Oxycontin® | 1 (8) | 2 (18) | 1 (5) |
| Sevredol® | 2 (15) | 1 (9) | 4 (21) |

THC = Δ9-tetrahydrocannabinol; CBD = cannabidiol.

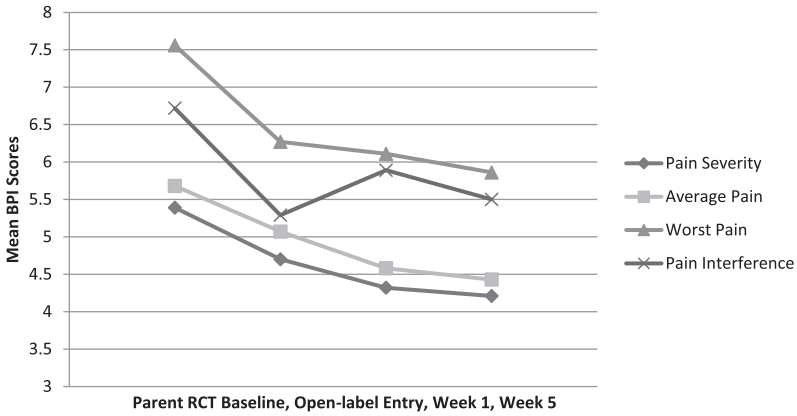



Fig. 2. Mean Brief Pain Inventory Short-Form (BPI-SF) scores for pain severity, average pain, worst pain, and pain interference domains.

*Safety and Tolerability*

All AEs with an incidence of 5% or more during this study are displayed in Table 3. The most commonly reported treatment-related AEs in the THC/CBD spray group were dizziness, nausea, vomiting, dry mouth, somnolence, and confusion. Only four patients were exposed to the THC study medication, with three treatment-related AEs reported by two of these patients including dizziness, headache, and an episode of memory impairment.

Twenty patients (51%) receiving THC/CBD spray developed at least one serious adverse event (SAE) during the study conduction, as did one patient (25%) receiving THC spray, but only three (8%) patients receiving THC/CBD spray had an SAE that was considered to be related to study medication. These three patients had other significant confounding factors, which should be considered when individually assessing each case. Study SAEs leading to death were observed in 12 patients (31%) receiving THC/CBD spray and one patient (25%) receiving THC spray; none of these deaths were considered to be treatment related. There also were six poststudy deaths reported, none of which were considered to be treatment related. Of the deaths that occurred during the study, all were reportedly caused by the patients' underlying cancer, with three incidences of patients who died of causes secondary to their cancer: one case of hematemesis secondary to malignant mesothelioma, one case of exacerbation of subacute bowel obstruction and progression of metastatic cervical carcinoma, and one case of renal

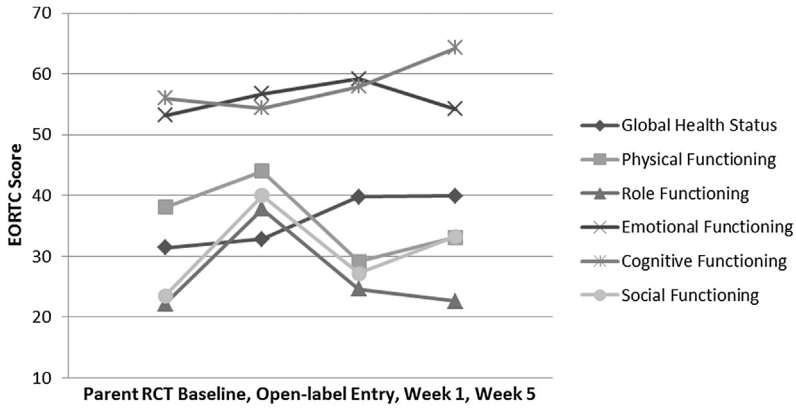



Fig. 3. Mean European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) scores for functional status domains.

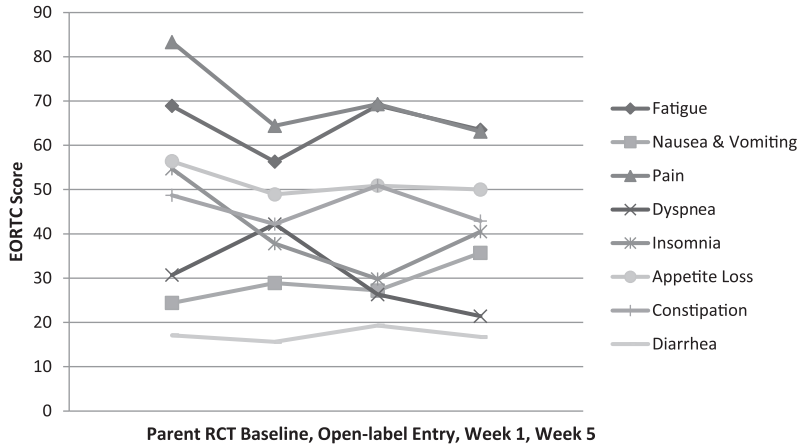



Fig. 4. Mean European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) scores for adverse symptom domains.

failure resulting from progression of the patients' tumor.

A total of 23 patients (59%) receiving THC/CBD spray and one patient (25%) taking THC spray withdrew because of AEs. Of these, 12 patients in the THC/CBD spray group had been previously randomized to the placebo treatment group in the parent RCT, accounting for around half of the withdrawals because of AEs in this treatment group. The THC spray

*Table 3*
**Number of Patients With at Least One AE With an Incidence of 5% or Greater by Preferred Term and System Organ Class, for All Causality and Treatment-Related AEs**

| System Organ Class/Preferred Term | THC/CBD Spray ($n = 39$), $n$ (%) | THC Spray ($n = 4$), $n$ (%) |
|---|---|---|
| Total subjects with at least one AE | 37 (95) | 4 (100) |
| Gastrointestinal disorders | 21 (54) | 1 (25) |
| Nausea | 7 (18) | 0 |
| Vomiting | 5 (13) | 0 |
| Dry mouth | 5 (13) | 0 |
| Diarrhea | 1 (3) | 0 |
| Nervous system disorders | 18 (46) | 3 (75) |
| Dizziness | 8 (21) | 1 (25) |
| Somnolence | 5 (13) | 0 |
| Headache | 1 (3) | 1 (25) |
| Memory impairment | 0 | 1 (25) |
| Neoplasms benign, malignant, and unspecified | 16 (41) | 2 (50) |
| Psychiatric disorders | 16 (41) | 1 (25) |
| Confusion | 5 (13) | 0 |
| Infections and infestations | 11 (28) | 2 (50) |
| Musculoskeletal and connective tissue disorders | 12 (31) | 1 (25) |
| Pain in limb | 2 (5) | 0 |
| Arthralgia | 1 (3) | 0 |
| General disorders and administration site conditions | 9 (23) | 0 |
| Renal and urinary disorders | 7 (18) | 1 (25) |
| Investigations | 8 (21) | 1 (25) |
| Respiratory, thoracic, and mediastinal disorders | 6 (15) | 0 |
| Dyspnea | 2 (5) | 0 |
| Blood and lymphatic system | 6 (15) | 0 |
| Metabolism and nutrition disorders | 5 (13) | 0 |
| Skin and subcutaneous tissue disorders | 3 (8) | 1 (25) |
| Injury, poisoning, and procedural complications | 3 (8) | 1 (25) |
| Vascular disorders | 2 (5) | 1 (25) |
| Hepatobiliary disorders | 1 (3) | 1 (25) |

AE = adverse event; THC = Δ9-tetrahydrocannabinol; CBD = cannabidiol.

patient who withdrew as a result of AEs had previously received THC/CBD spray in the parent RCT.

## Discussion

Chronic and unrelieved pain in cancer can cause significant distress and disability.[28,29] This study has been valuable in providing insight into the long-term benefit, safety, and tolerability of THC/CBD spray, with BPI-SF and EORTC QLQ-C30 data suggesting maintenance of benefit with long-term use. There are difficulties in interpreting efficacy evaluations from open-label, noncomparative, long-term studies. A patient's decision to remain in the study could suggest that the perceived benefit outweighs any negative effects for that patient; examination of the study duration and of the reasons for exiting can be informative in this respect. In this study, the diminishing numbers of patients providing data over time were, in general, not the result of patient withdrawal, but rather were reflective of the ongoing staggered recruitment into this study from the preceding parent RCT,[25] up to the time the study was stopped. The attrition rate also was impacted by the number of deaths from the underlying illness that occurred during the study, which totaled 13. As such, interpreting the time course of any efficacy parameter in a noncomparative study in which the patients are self-selecting and the size of the population is declining is problematic. Any observed patterns may be the result of a variety of reasons, including disease progression or regression, changing patient population, efficacy-related issues, or a combination of these factors. Consequently, care should be exercised in drawing conclusions from this study.

Patients in this study were diagnosed with pain related to terminal cancer that was not fully relieved by the current strong opioid analgesia. The most common pain type reported for patients in this study was mixed, followed by neuropathic. Although limited efficacy data were collected because of the acknowledged limitations of this study design, there is some indication from the BPI-SF and EORTC QLQ-C30 data that the benefits received by study patients during the randomized study[25] were maintained during their participation in the extension study, without an increase in the dose of the study medication. This was seen most notably in domains of the EORTC QLQ-C30 relating to pain and insomnia, and in the "pain severity" and "worst pain" sections of the BPI-SF. Clearly, for patients with cancer-related pain, pain is a major issue and its interrelationship with sleep is well documented. The lack of evidence of deterioration in these two important domains in this population of terminal patients is very positive. A possible basis for this benefit has been demonstrated in animal models showing that CBs can interact synergistically with opioid receptor agonists in the production of antinociception.[17–19,30] This suggests that the adjuvant use of CBs in patients with cancer-related pain, where most patients experience mixed nociceptive and neuropathic type pain, could provide enormous benefit. This suggestion also was supported by a recent clinical study, which found that THC/CBD spray had analgesic efficacy when used as an add-on therapy in cancer patients whose pain responded poorly to opioids. Although the primary efficacy measure of 30% responder analysis did not reach statistical significance, a secondary continuous responder analysis of average daily pain from baseline to end of study demonstrated that the proportion of patients reporting analgesia was greater for THC/CBD spray than placebo overall.[31] There was a suggestion from the EORTC QLQ-C30 data of deterioration in physical function in the patients who remained in the study, although the limitations of the study design did not allow a determination of whether this was secondary to progression of terminal disease, concomitant medicines, or study medication. The lack of information regarding concomitant levels of opioid analgesic during the extension study represents a possible weakness in the analysis of both this deterioration in condition and in efficacy.

Despite the relatively high proportion of investigators who considered pain management to be suboptimal at each study visit, the results of this study demonstrate that both patients and investigators considered that maintenance of treatment with THC/CBD spray was justified by the clinical importance of the effect in the target population. This is reflected by the fact that most patients remained in the study for over two weeks and only three (7%)

withdrew because of the lack of efficacy. The apparent discrepancy between patient continuation within the study and investigators' lack of satisfaction with the level of pain relief may be because patients with cancer-related pain are often satisfied with analgesics that cause pain to remain at levels that physicians may consider unacceptable.[32] A clinically important difference can be defined as the smallest difference in score that patients perceive as beneficial and that would mandate, in the absence of troublesome side effects, a change in the patient's management.[33,34] The fact that only a small proportion of patients withdrew from the study because of the lack of efficacy suggests, therefore, that patients considered the study medication to be providing a clinically meaningful benefit.

The most commonly reported treatment-related AEs in the THC/CBD spray treatment group were dizziness, nausea, vomiting, dry mouth, somnolence, and confusion. These AEs have been observed in other clinical studies with THC/CBD spray and are recognized as having a possible plausible causal relationship to the study medication.[21,23,24] It is difficult to draw conclusions from the data because there is no comparative information available and there are likely to be competing etiological factors involved in this group of patients with underlying malignancy. Only four patients were exposed to THC, and there were only three treatment-related AEs reported by two of these patients, including dizziness, headache, and an episode of memory impairment. Only three patients had an SAE that was considered to be related to study medication, all receiving THC/CBD spray. All three patients who reported treatment-related SAEs had other significant confounding factors. There were 19 deaths reported during the treatment period of the study (including six poststudy deaths), confirming that the study population had pain associated with advanced illness. None of these deaths were considered to be related to study medication.

Despite the methodological limitations of the study design, it has been possible to observe some important patterns across the safety and efficacy parameters over time. The results suggest that THC/CBD spray remains well tolerated and beneficial for up to five weeks of exposure. In addition, there was an implicit suggestion of continued efficacy for longer periods from the patients who elected to continue to receive the study medication. Notably in this population with terminal disease, study medication was taken for more than six months by 10% of patients and for more than one year by 5% without requiring dose escalation. In summary, the findings show that some patients will continue to obtain relief of cancer-related pain with long-term use of THC/CBD spray, without increasing their dose of this or other pain-relieving medications over time, suggesting that the adjuvant use of THC/CBD spray in cancer-related pain could provide substantial benefit to patients.

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