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Nabiximols for Opioid-Treated Cancer Patients With Poorly-Controlled Chronic Pain: A Randomized, Placebo-Controlled, Graded-Dose Trial

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Abstract: **Patients with advanced cancer who have pain that responds poorly to opioid therapy pose a clinical challenge. Nabiximols (Nabiximols is the US Adopted Name [USAN] for Sativex [GW Pharma Ltd, Wiltshire, UK], which does not yet have an INN), a novel cannabinoid formulation, is undergoing investigation as add-on therapy for this population. In a randomized, double-blind, placebo-controlled, graded-dose study, patients with advanced cancer and opioid-refractory pain received placebo or nabiximols at a low dose (1–4 sprays/day), medium dose (6–10 sprays/day), or high dose (11–16 sprays/day). Average pain, worst pain and sleep disruption were measured daily during 5 weeks of treatment; other questionnaires measured quality of life and mood. A total of 360 patients were randomized; 263 completed. There were no baseline differences across groups. The 30% responder rate primary analysis was not significant for nabiximols versus placebo (overall *P* = .59). 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 nabiximols than placebo overall (*P* = .035), and specifically in the low-dose (*P* = .008) and medium-dose (*P* = .039) groups. In the low-dose group, results were similar for mean average pain (*P* = .006), mean worst pain (*P* = .011), and mean sleep disruption (*P* = .003). Other questionnaires showed no significant group differences. Adverse events were dose-related and only the high-dose group compared unfavorably with placebo. This study supports the efficacy and safety of nabiximols at the 2 lower-dose levels and provides important dose information for future trials.**

Perspective: ***Nabiximols, a novel cannabinoid formulation, may be a useful add-on analgesic for patients with opioid-refractory cancer pain. A randomized, double-blind, placebo-controlled, graded-dose study demonstrated efficacy and safety at low and medium doses.***

Key words: *Cancer, pain, tetrahydrocannabinol, cannabidiol, nabiximols.*

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Chronic pain is highly prevalent in populations with advanced cancer. More than 10 million people annually are diagnosed with cancer worldwide, and this is likely to increase to more than 15 million per year by 2020.[32] Surveys indicate that more than 70% of those with advanced disease have moderate or severe chronic pain.[4,8] The management of chronic pain is an essential element in a comprehensive strategy for palliative care.[23]

Opioid therapy is the mainstay approach in the treatment of moderate or severe cancer pain associated with active disease.[2,12] Effective opioid therapy requires individualization of the dose in an effort to identify a favorable balance between analgesia and side effects.[11] Side effects are common[3,13,14] and a substantial minority experience pain that cannot be adequately controlled at a tolerated dose. These patients with poorly responsive pain must be offered an alternative strategy.[7,22] Among the most common is the coadministration of another analgesic, either a conventional nonopioid analgesic or one of the so-called adjuvant analgesics.[12] If effective, coadministration of another analgesic may increase analgesia and allow reduction of the opioid dose, with favorable results on side effects.

Cannabinoids are undergoing investigation as potential adjuvant analgesics. *Cannabis sativa* L. contains 60 or more cannabinoids, the most abundant of which are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD).[20] These and other cannabinoids presumably mimic the action of endogenous cannabinoid compounds (anandamide, 2-arachidonoyl glycerol [2-AG]), which act primarily via specific cannabinoid receptors. CB_1 receptors are predominantly distributed in the CNS; CB_2 receptors are more extensive in the periphery, especially the immune system.[21] THC, a partial CB_1 and CB_2 receptor agonist, may produce psychoactive effects, analgesia, muscle relaxation, anti-emesis, and appetite stimulation.[19,21] CBD also has analgesic and anti-inflammatory effects, and has been shown to reduce the anxiogenic and psychoactive effects of THC.[10,33]

In animal studies, cannabinoids and opioids have synergistic analgesic effects in both acute and chronic pain models.[5,24,27,30] The mechanism of this synergy is unclear, and a variety of potential mechanisms have been postulated.[5] Cannabinoid and opioid receptors colocalize in brain and spinal cord areas relevant to descending pain pathways and cannabinoids provoke the release of endogenous opioid precursors.[31] These studies provide a rationale for the development of cannabinoid drugs as adjuvant analgesics in opioid-treated patients. Studies of these compounds to date suggest that they may be able to enhance the analgesic efficacy of opioids, but the investigations are short-term and in small samples.[6]

Nabiximols (Sativex; GW Pharma Ltd., Wiltshire, UK) is a standardized extract of *Cannabis sativa* L. that contains THC and CBD at a fixed ratio. Delivered as an oromucosal spray, each 100 μL delivers 2.7 mg of THC and 2.5 mg of CBD. Nabiximols has been shown to have analgesic efficacy in peripheral neuropathic pain[17] and both pain and spasticity resulting from multiple sclerosis.[16,25,29] A small study in cancer pain also suggested benefit.[9] The doses administered in these studies may or may not be optimal in a larger population of opioid-treated patients, given the potential for synergistic effects between nabiximols and the opioid. This controlled trial was designed to address the need for more data to ensure that dose selection for a definitive study of safety and efficacy would explore the optimal dose range. The aim was to obtain information about the dose response for analgesia and safety in a population with medical illness and pain that is not adequately controlled with an opioid.

Methods

Design

This multicenter study used a randomized, double-blind, placebo-controlled, parallel group, graded-dose design to evaluate the analgesic efficacy and safety of nabiximols in 3 dose ranges. The design is summarized in Fig 1. The study timeline included a 5- to 14-day baseline period, a 5-week titration and treatment period, and a poststudy visit after 2 weeks. The maximum duration was 9 weeks.

The study was approved by the Ethical Committees or Institutional Review Boards at each study site. The study was conducted within Good Clinical Practice guidelines.

Inclusion and Exclusion Criteria

Adult patients were eligible for the study if they had active cancer and chronic pain that was moderate or severe despite a stable opioid regimen that could not be made more effective by further opioid dose titration. The latter judgment was based on the current experience of side effects, or a previous experience with side effects at a higher dose. The opioid regimen consisted of an oral modified-release opioid formulation or transdermal fentanyl. Patients receiving long-term methadone therapy for pain were not eligible because of concerns that its potency relative to other opioid agonists may vary with dose, rendering analyses using morphine equivalent milligrams less reliable. All other opioids typically used for severe cancer pain were allowed.

Patients were excluded from study participation if they had a major psychiatric or cardiovascular disorder, epilepsy, or significant renal or hepatic impairment, or if they were pregnant, lactating or not using adequate contraception. Patients who had received or who were due to receive therapies that were expected to change the pain (such as radiotherapy, or chemotherapy or hormonal therapy) also were excluded. Patients who were currently using or had used marijuana, cannabinoid-based medications or rimonabant within 30 days of study entry, and were unwilling to abstain for the duration of the study, were excluded.

Procedures

Potentially eligible patients were identified from medical records. With the assent of their treating oncologists, interested patients were asked to participate in a screening visit. At the screening visit, written informed consent was obtained. The history and records were reviewed and patients were examined. Laboratory testing was reviewed and additional testing was done if needed.

Those patients who continued to meet inclusion and exclusion criteria began a qualifying period, which was 5 to 14 days long. If needed, the opioid regimen could

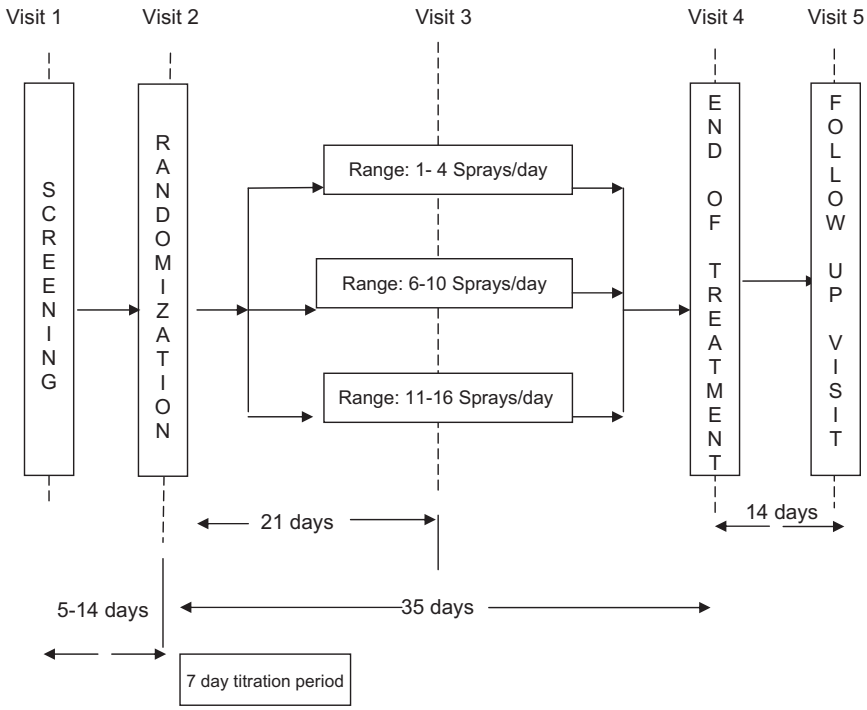

Figure 1. Study design.

be adjusted in an effort to optimize the balance between analgesia and side effects. The patients received a daily call from an interactive voice recording system (IVRS), at which time they were asked to grade their average pain during the past day using a 0 to 10 numeric rating scale (NRS). In order to be eligible for randomization, the opioid regimen had to remain stable and scores for average pain had to be ≥4 and ≤8 on the NRS, and not change by more than 2 points, over 3 consecutive days. These 3 days were used for analyses that included the baseline period. Patients who could not meet criteria for the randomization by 14 days were discontinued from the study.

After randomization, patients entered a titration and treatment phase, which included a 1-week blinded dose titration period followed by 4 weeks of stable dosing. Throughout this phase, patients self-administered the study drug (either nabiximols or an identically-appearing placebo) as an oromucosal spray delivered using a pump. Each actuation of the nabiximols pump delivered 100 μL of fluid to the oral mucosa. Each active dose contained 2.7 mg THC and 2.5 mg CBD; each placebo dose contained only excipients plus colorants.

Patients were randomly assigned by computer using a block approach, first to 1 of 3 dose groups, and then within each group, to either active drug or placebo. The allocation to active drug or placebo was in a 3:1 ratio. The randomization was stratified by region (North America/Rest of the World). Patients randomly assigned to Group 1 (low dose) were instructed to titrate the study medication to between 1 and 4 sprays per day. Those assigned to Group 2 (medium dose) titrated the number of sprays to between 6 and 10 sprays per day, and those assigned to Group 3 (high dose) titrated to between 11 and 16 sprays per day.

During the 1-week titration period, a schedule specific for each group was followed (Table 1). In all groups, patients followed the titration schedule until they achieved the maximum target dose for the specific dose range, unless intolerable side effects prevented further dose escalation. Patients who were unable to reach the minimum target dose in the dose range to which they had been randomized were discontinued from the study.

After the 1-week titration period, the daily dose of the study medication was kept stable, unless exigent clinical

Table 1. Dose Titration Regimen

Day	Low Dose Max. Sprays/Day	Medium Dose Max. Sprays/Day	High Dose Max. Sprays/Day
1	1	1	2
	am : pm	am : pm	am : pm
	0:1	0:1	0:2
2	2	2	4
	am : pm	am : pm	am : pm
	1:1	1:1	1:3
3	3	3	6
	am : pm	am : pm	am : pm
	1:2	1:2	2:4
4	4	4	8
	am : pm	am : pm	am : pm
	1:3	1:3	2:6
5	4	6	10
	am : pm	am : pm	am : pm
	1:3	2:4	3:7
6	4	8	11
	am : pm	am : pm	am : pm
	1:3	2:6	3:8
7	4	10	16
	am : pm	am : pm	am : pm
	1:3	3:7	5:11

problems prevented this. Stable dosing continued for 4 weeks. All doses taken were recorded daily by patients via an IVRS. Compliance and adherence were carefully monitored and any discrepancies discussed with the patient.

Throughout the entire titration and treatment phase, patients were asked to continue their scheduled opioid dose without change. They were allowed to use their breakthrough opioid analgesic as required.

Measures

Each day of the study, patients interacted with the IVRS and were asked to respond to several questions:

1. "On a scale of '0 to 10,' please indicate the number that best describes your pain on average in the last 24 hours" where 0 = no pain and 10 = pain as bad as you can imagine.
2. "On a scale of '0 to 10,' please indicate the number that best describes your worst pain in the last 24 hours" where 0 = no pain and 10 = pain as bad as you can imagine:" for both of these questions, patients were instructed to relate no pain to the time prior to the onset of their pain from cancer.
3. "On a scale of '0 to 10,' please indicate how your pain disrupted your sleep last night?" where 0 = did not disrupt sleep and 10 = completely disrupted (unable to sleep at all).
4. "How many sprays of study medication have you taken since you called yesterday?"
5. "Have you taken your fixed-dose painkiller today as prescribed?"
6. "How many doses of breakthrough painkiller have you taken since you called yesterday?"

Patients also completed a questionnaire packet at the time of randomization and at the study termination visit. The questionnaires were selected to measure a range of issues relevant to the quality of life of patients with advanced cancer. The packet included the Brief Pain Inventory-Short Form (BPI-SF), the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) Version 3,[1] the Patient Assessment of Constipation Quality of Life (PAC-QoL),[13] and the Montgomery-Åsberg Depression Rating Scale (MADRS).[15] Patients also completed a Patient Global Impression of Change (PGIC)[26] at the study termination visit. The BPI-SF was selected because it is a validated, widely used, self-administered questionnaire developed to assess the severity of pain and the impact of pain on daily functions. The EORTC questionnaire was selected because it is designed to be cancer specific, multidimensional in structure, appropriate for self-administration, and applicable across a range of cultural settings.[1] The PAC-QoL questionnaire is a brief but comprehensive assessment of the burden of constipation on patients' everyday functioning and well-being; multinational studies have demonstrated that it is internally consistent, reproducible, valid, and responsive to improvements over time.[13]

Adverse events (AEs) and use of concomitant medications were reported by patients at study visits throughout the trial. Study physicians determined the AEs' intensity and relationship to study medication using predefined standard descriptors.

Statistical Analysis

The study was powered based upon the findings of a previous placebo-controlled study in patients with cancer pain. In terms of defined analgesic response, this study favored nabiximols, with an odds ratio of 2.67.[9] It was estimated that the response rate in the placebo group would be approximately 20%, leading to a response rate of approximately 40% in the active drug group. It also was assumed that the placebo patients randomized to each cohort could be pooled for the analyses of efficacy, so that the overall allocation ratio for the 4 study treatments would be 1:1:1:1. Given these assumptions, 84 patients randomized to each treatment group would have 80% power to detect an increase of 20% in the response rate with nabiximols at a significance level of 5%. This calculation meant that 336 patients were required to be randomized to the 4 treatment groups (122 in each dose cohort and 84 in each treatment group).

The efficacy analyses were intent-to-treat. All patients who were randomized and received at least 1 dose of study medication were entered into the analyses. Missing data for the efficacy endpoints were imputed using the last observation carry forward (LOCF) method.

The primary efficacy endpoint was chosen to be pain response status, with a positive response defined as a 30% or greater reduction in the mean 11-point NRS pain score for average pain during the last 3 days of week 5 compared with the mean during the 3-day baseline period. This 30% responder analysis was supplemented by a continuous responder analysis, which evaluated the differences between placebo and active drug in the proportion of patients who achieve levels of response that range from 0% to 100% at predefined levels (eg, 10%, 20%, and so on, again comparing week 5 versus baseline). Other pain endpoints included the change in the mean daily NRS score for average pain and the change in the mean daily NRS pain score for worst pain.

The proportions of responders were compared between the treatments using logistic regression, with region (North America/Rest of the World) and treatment used as factors. The primary comparisons of interest were each of 3 active treatments versus placebo. The assumption that the response in the placebo groups for the 3 dose cohorts was similar was tested by fitting a logistic regression model to the primary endpoint and including cohort and region as factors. The overall test of cohort was used to test the assumption of poolability, with the test rejected if the *P* value was significant at the 10% level. The accepted data were then pooled for the analysis of efficacy.

The cumulative response to treatment was shown by plotting cumulative response rates against increasing thresholds for response, ie, percentage changes from baseline in the mean 11-point NRS pain score that

defined a response. The cumulative response curves for each of the active treatment groups were compared with placebo using pairwise Wilcoxon rank-sum tests. The Hodges-Lehmann estimates and 95% CI for the median also were performed.

Efficacy also was evaluated by comparing placebo and active treatment in terms of the proportion of patients showing a response on an opioid composite measure from baseline to the end of week 5. The opioid composite measure was calculated using both the change in the patient's average pain NRS and the change in their opioid consumption converted into morphine equivalent milligrams. It defined a positive response as either a reduction in pain with a stable or decreasing opioid consumption, or a reduction in the opioid consumption with a decreasing or stable pain score. Other secondary outcomes were evaluated using the validated measures in the questionnaire packet; these were assessed in terms of the change from baseline to end of study.

The analysis of all the secondary efficacy assessments was considered supportive and no formal adjustments for multiple comparisons were made. The change in mean pain NRS scores, BPI-SF, sleep disruption NRS, PAC-QoL questionnaire, and MADRS were all analyzed using analysis of covariance (ANCOVA), with the baseline value as a covariate and region and treatment group as factors. An analysis also was performed on the mean pain NRS scores to assess the time course of the treatment effect using repeated measure analysis. Additionally, the difference in time required to establish baseline was investigated as a possible moderator of treatment effect by using the number of days until the patient became eligible for randomization and total number of days in the baseline period as covariates in the analysis of change in the mean daily NRS score for average pain.

The PGIC was collected once at the end of treatment and was analyzed with ordinal logistic regression using the proportional odds model, with baseline as a covariate and region and treatment as group factors.

Results

A total of 503 patients were screened over 24 months in 84 study centers across North America, Europe, Latin America, and South Africa. Three hundred and sixty patients were randomized and 97 (27%) discontinued prior to study completion. The proportion and reasons for discontinuation did not vary across dose groups (Fig 2). A total of 263 patients completed the study, including 71, 67, and 59 patients assigned to the low-, medium-, and high-dose groups, respectively, and 66 patients who received placebo.

Randomized patients had a mean age of 58 (±12.2) years and 174 (48.3%) were male (Table 2). The characteristics of the patients in the various treatment groups were similar. Patients had cancer for a mean of 3.6 (±4.8) years. The most common sites were gastrointestinal, lung, breast, and prostate. All patients had chronic pain, with the most common type labeled as mixed (42%), followed by bone (24%), visceral (15%), and neuropathic (11%) (Table 3). At baseline, the median (range) daily dose of opioid background medication was equivalent to 120 mg (range 0–16,660 mg) of oral morphine.

Both the number of days until eligibility was reached and the total number of days in the baseline period were similar among all 3 nabiximols dose groups and placebo. The median time until eligibility was 3 days for all groups and the range was 2 to 15; the median total days prior to randomization was 7 for all groups, with a range of 4 to 20.

There were no major discrepancies during the study and compliance was good. At the end of treatment, there was a notable pattern of underdosing particularly in the nabiximols treatment groups, where the proportion of patients who were not taking the targeted dose increased markedly as the target increased. At the end of treatment, only 62.2% of patients in the high nabiximols dose group were taking sprays within their assigned dose range, compared to the majority of patients randomized to the nabiximols low- (94.5%) and medium- (85.1%) dose groups.

Pain Responses

There were no significant differences in pain response among different dose groups that were randomized to placebo (P = .84) and the placebo groups were, therefore, pooled for comparison with active drug. The primary endpoint of the proportion of patients reporting 30% relief from baseline pain at the end of the study, ie, the 30% responder rate analysis, was not statistically different between active drug and placebo (P = .59). In contrast, a broader analysis of responder rates using the secondary endpoint of continuous responder rates, which compares the proportion of responders (active drug versus placebo) across the full spectrum of response (0–100%), demonstrated a treatment effect in favor of the combined nabiximols groups (P = .035) (Fig 3). Examination of the individual nabiximols dose groups showed that the effect was significant only in the 2 lower dose groups (P = .008 and .038, respectively). When the low and medium groups were combined, there was an estimated median difference between treatment groups of 10.5% in favor of nabiximols.

Additional analyses were conducted to determine differences in mean pain responses. The mean baseline pain scores were comparable among the 3 dose groups and placebo. There was some evidence of a significant overall treatment effect when the nabiximols dose groups were combined. (P = .072). Again, this overall treatment effect was the result of improvement in pain scores with the lower 2 nabiximols dose groups (Fig 4). The adjusted mean change in pain score for the group titrated to 1 to 4 sprays per day was −1.5 points on the 11-point NRS (from a mean baseline score of 5.8 points), compared to a change of −.8 points from a mean baseline score of 5.7 points among placebo-treated patients. This represented a treatment difference of −.75 points in favor of nabiximols (P = .006, 95% CI: −1.28, −.22 points). The adjusted mean change in the score for the medium-dose

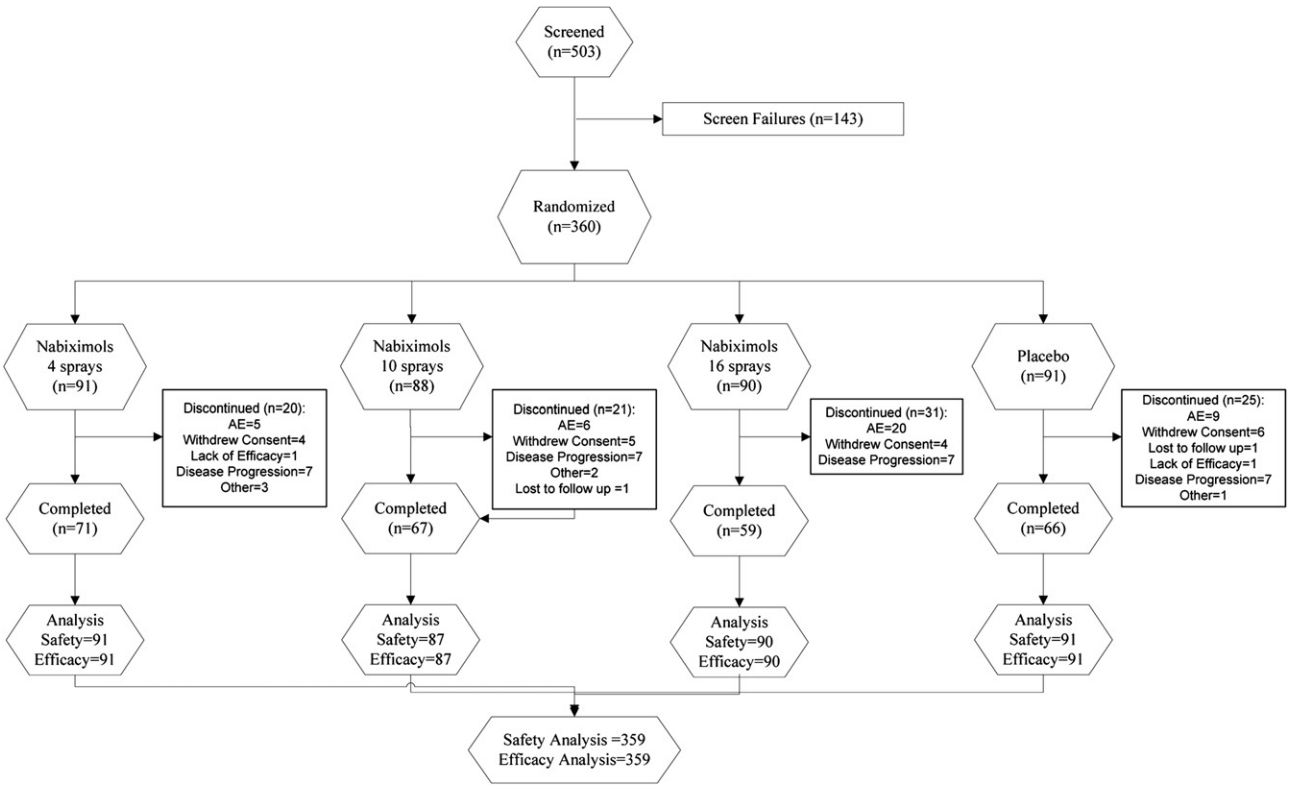

Figure 2. Study design CONSORT diagram.

group was −1.1 points from a mean baseline of 5.8 points, or a treatment difference of −.36 points compared to the placebo-treated patients: this was not statistically significant (P = .19, 95% CI: −.89, .18 points). There was no difference between the high-dose group and placebo (P = .75, 95% CI: −.62, .44 points). When a post hoc analysis was performed to combine the low and medium groups, there was a treatment difference in mean pain of −.55 points in favor of nabiximols (P = .019). Neither the number of days until eligibility was reached nor the total number of days in the baseline period were moderators of the treatment effect of change from baseline in average pain NRS score; a statistically significant effect was still shown with the low-dose nabiximols (P = .006 and P = .005, respectively).

To evaluate the weekly evolution in the change in pain, the change in weekly mean pain on average scores relative to baseline was compared across groups. In the low-dose group, the mean change in pain score showed the greatest reduction at week 5, at which time the mean score was −1.4 points less than the mean baseline score of 5.8 points. For the corresponding period, the placebo treatment group showed a reduction of −.8 points from a mean baseline score of 5.7 points. This represented a treatment difference of −.59 points in favor of nabiximols (P = .024, 95% CI: −1.11, −.08 points). The medium-dose group at week 5 showed a reduction of −1.2 points from a mean baseline score of 5.8 points, representing a treatment difference from placebo of −.36 points in favor of nabiximols (P = .178, 95% CI: −.88, .16 points). There were no differences observed between the nabiximols high-dose group and placebo; the adjusted mean change in pain score for the high-dose group at week 5 showed a reduction of −1.0 points from a mean baseline score of 5.8 points (P = .555, 95% CI: −.67, .36 points). When the low and medium groups were combined, there was an estimated mean treatment difference of −.47 points in favor of nabiximols (P = .039).

Daily worst pain scores also were analyzed across treatment groups. At the end of treatment, there was evidence of an overall treatment effect (P = .047). As with the previous findings, this effect was predominantly a result of the improvement in pain score with the low-dose group; for this group, there was a reduction of −1.6 points from a mean baseline score of 6.9 points, giving a treatment difference of −.73 points in favor of nabiximols (P = .011, 95% CI: −1.30, −.17 points). The medium-dose group showed a reduction of 1.1 points for nabiximols (P = .40, treatment difference = −.24, 95% CI: −.8, .3 points) (Table 4). Like the medium-dose group, the high-dose group showed a greater but nonsignificant reduction in pain among those treated with the nabiximols (reduction of .9 points from a mean baseline score of 6.9 points, P = .83, 95% CI: −.6, .5 points).

Sleep Disruption

The sleep disruption NRS was completed daily in the evening. The mean baseline sleep disturbance scores were comparable among the 3 dose groups and the placebo group. At the end of treatment, there was evidence of an overall treatment effect (P = .012). Again, this was predominantly the result of the improvement in sleep disturbance score within the low-dose group (Table 4).

Table 2. Demographics

	Number (Percentage) of Patients				
	Nabiximols 1–4 Sprays (N = 91)	Nabiximols 6–10 Sprays (N = 88)	Nabiximols 11–16 Sprays (N = 90)	Placebo (N = 91)	Total (N = 360)
Gender					
Male	45 (49.4)	49 (55.7)	48 (53.3)	44 (48.3)	186 (51.7)
Female	46 (50.5)	39 (44.3)	42 (46.7)	47 (51.6)	174 (48.3)
Ethnic origin					
Caucasian	67 (73.6)	74 (84.1)	68 (75.6)	69 (75.8)	278 (77.2)
Black	11 (12.1)	6 (6.8)	10 (11.1)	6 (6.6)	33 (9.2)
Hispanic	10 (11.0)	7 (8.0)	7 (7.8)	12 (13.2)	36 (10.0)
Asian	0	1 (1.1)	1 (1.1)	0	2 (.6)
Other	3 (3.3)	0	4 (4.4)	4 (4.4)	11 (3.1)
Previous cannabis use	11 (12.1)	11 (12.5)	10 (11.1)	6 (6.6)	38 (10.6)
	Mean (SD)				
Age (years)	59 (12.3)	59 (13.1)	58 (11.2)	56 (12.2)	58 (12.2)
(range)	(20, 88)	(27, 93)	(25, 81)	(20, 83)	(20, 93)
BMI (kg/m2)	24.6 (5.3)	25.4 (6.3)	25.6 (7.2)	24.9 (6.1)	25.1 (6.2)
(range)	(15, 42)	(15, 48)	(15, 58)	(13, 41)	(13, 58)
Duration of cancer (years)	3.6 (5.2)	3.0 (3.5)	3.5 (4.3)	4.3 (5.9)	3.6 (4.8)
(range)	(.033, 27.362)	(.003, 16.041)	(.071, 18.661)	(.088, 42.861)	(.003, 42.861)
Average pain at baseline	5.8 (1.3)	5.8 (1.2)	5.8 (1.2)	5.7 (1.2)	5.8 (1.2)
(range)	(4, 8)	(4, 8)	(4, 8)	(4, 8)	(4, 8)
Duration of pain (years)	1.7 (3.1)	1.8 (2.8)	1.7 (2.1)	2.4 (3.2)	1.9 (2.8)
(range)	(.027, 19.181)	(.030, 16.041)	(.049, 9.478)	(.036, 16.290)	(.027, 19.181)
Fixed dose opioids*	120	120	180	120	120
(range)	(3, 16660)	(0, 2040)	(0, 2520)	(0, 1104)	(0, 16660)

*Median dose expressed as morphine equivalent milligrams.

For this group, there was a treatment difference of −.88 points in favor of nabiximols (P = .003 95% CI: −1.45, −.31 points). In the medium-dose group, there was a non-significant treatment difference of −.33 points in favor of nabiximols (P = .260 95% CI: −.90, .24 points), and there were no differences between the high-dose group and placebo. When the low and medium groups were combined, there was a treatment difference from placebo of −.61 points in favor of nabiximols (P = .016, 95% CI: −1.1, −.1 points).

Opioid Usage

Neither the use of regularly scheduled opioids nor the number of opioid doses taken as needed for breakthrough pain varied significantly between treatment groups. Using the opioid composite score, more patients

Table 3. Primary Cancer Site and Pain Classification

	Number (Percentage) of Patients				
	Nabiximols 1–4 Sprays (N = 91)	Nabiximols 6–10 Sprays (N = 88)	Nabiximols 11–16 Sprays (N = 90)	Placebo (N = 91)	Total (N = 360)
Primary cancer sites					
Breast	15 (16.5)	11 (12.5)	15 (16.7)	13 (14.3)	54 (15.0)
Gastrointestinal	15 (16.5)	17 (19.3)	16 (17.8)	16 (17.6)	64 (17.8)
Lung	13 (14.3)	17 (19.3)	14 (15.6)	20 (22.0)	64 (17.8)
Prostate	10 (11.0)	8 (9.1)	14 (15.6)	12 (13.2)	44 (12.2)
Other	35 (38.5)	30 (34.1)	28 (31.1)	29 (31.9)	122 (33.9)
Unknown	3 (3.3)	5 (5.7)	3 (3.3)	1 (1.1)	12 (3.3)
Pain classification					
Bone	20 (22.0)	15 (17.0)	34 (37.8)	17 (18.7)	86 (23.9)
Mixed	42 (46.2)	37 (42.0)	32 (35.6)	39 (42.9)	150 (41.7)
Neuropathic	8 (8.8)	12 (13.6)	7 (7.8)	11 (12.1)	38 (10.6)
Somatic	1 (1.1)	13 (14.8)	7 (7.8)	11 (12.1)	32 (8.9)
Visceral	20 (22.0)	11 (12.5)	10 (11.1)	13 (14.3)	54 (15.0)

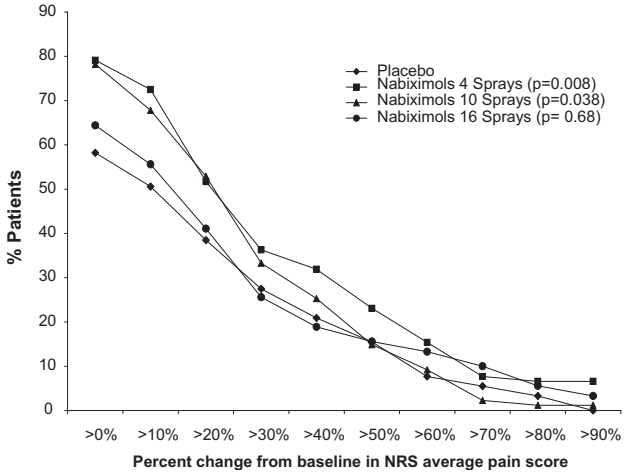

Figure 3. Continuous responder analysis.

in the 3 nabiximols groups showed a better responder profile compared to those in the placebo group (54% versus 43%) (odds ratio = 1.54; 95% CI: .95, 2.50) (Table 4). This result approached statistical significance (P = .077). Patients in the low-dose group showed statistical superiority to placebo (58% versus 43%; P = .038). Patients in the medium group were not significantly superior to placebo (56% versus 43%; P = .079). There was no difference between nabiximols and placebo in the high-dose group. When the low and medium-dose groups were combined, there was a positive treatment effect, with the nabiximols group again superior to placebo (57% versus 43%; P = .050).

Other Measures

There were no notable treatment differences between the nabiximols groups and the placebo group on the BPI-SF, the PGIC score, the PAC-QoL, or the MADRS (Table 4). Results from the EORTC QLQ-C30 showed that nabiximols treatment had little effect on the majority of subscales when compared with placebo. Nabiximols treatment did impact the cognitive functioning dimension of the scale negatively. Also, a significant proportion of patients experienced nausea and vomiting in the nabiximols groups compared with placebo (treatment difference of 7.57, P = .019); however, this result was driven mainly by patients in the high-dose group (P = .009).

Adverse Events

The overall frequency of AEs is shown in Table 5 and details of AEs that occurred with a frequency of more than 5% are provided in Table 6. There was a dose-related incidence of AEs, with the high-dose group comparing unfavorably with placebo and the 2 lower dose groups showing little difference from placebo. The number of treatment emergent AEs per patient was 4.0, 4.3, and 4.1 for the low-dose, medium-dose and high-dose groups, respectively, compared with 3.1 for the placebo group.

Discontinuations from study treatment were also dose related, with a higher rate (27.8%) in the high-dose group compared with the low-dose group (14.3%), medium-dose group (17.2%), and placebo (17.6%). Serious adverse events (SAEs) were somewhat more common in the low-dose group. A summary of the SAEs and deaths according to dose group is shown in Table 7; the relatively high incidence reflects a population with advanced cancer. In total, 29.5% of the nabiximols-treated patients experienced an SAE, compared with 24.2% of the placebo group. Overall, 20.9% of all patients randomized to receive nabiximols died during the study, compared with 17.6% of placebo patients. None of these deaths were considered to be related to the study medication. The highest incidence of death was seen in the neoplasms System Organ Class. The number of deaths in the low-dose group was higher than that in the other groups, which was an unanticipated finding. A post hoc analysis was performed that identified 4 baseline risk factors (high white blood cell levels, and low calcium, hemoglobin and lymphocyte levels) as potential confounding causes. Analysis of the data by an independent Safety Monitoring Committee for the study concluded that "most deaths appeared to be due to disease progression" and that "there does not seem to

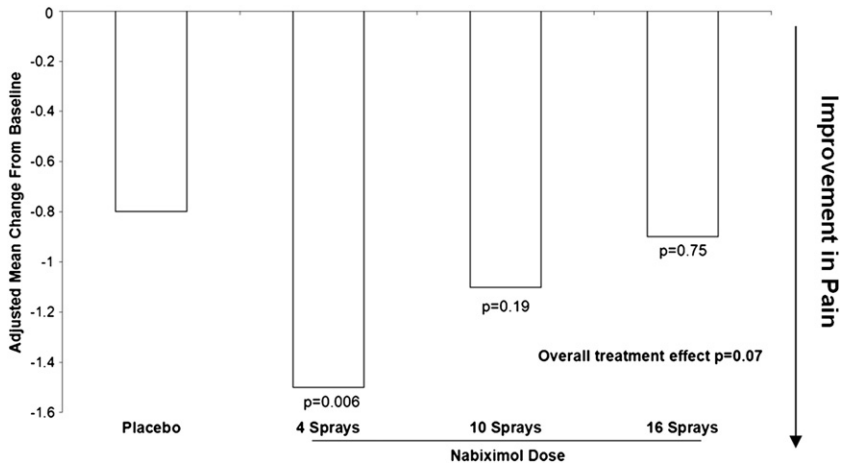

Figure 4. Analysis of change from baseline in NRS average pain score.

Table 4. Summary of Main Efficacy Results

	Treatment Difference/Odds Ratio (P value)		
	Nabiximols 1–4 Sprays	Nabiximols 6–10 Sprays	Nabiximols 1–16 Sprays
30% Responder rate analysis	1.37 (.33)*	1.19 (.61)*	.90 (.76)
Cumulative responder analysis	−12.5 (.008)*	−8.75 (.038)*	−1.97 (.675)*
Daily average pain NRS	−.75 (.006)*	−.36 (.187)*	−.09 (.750)*
Daily mean worst pain NRS	−.73 (.011)*	−.24 (.397)*	−.06 (.829)*
Sleep disruption NRS	−.88 (.003)*	−.33 (.260)*	−.08 (.784)*
BPI-SF pain severity composite score	−1.30 (.236)*	−1.40 (.119)*	−1.00 (.861)*
BPI-SF pain interference composite score	−.90 (.871)*	−1.50 (.088)*	−.90 (.956)
PAC-QoL overall score	−.10 (.226)*	−.10 (.493)*	.00 (.139)*
PGIC	1.40 (.268)*	.88 (.664)	.83 (.538)
MADRS	−2.40 (.480)	−1.50 (.151)	−1.10 (.083)
Opioid composite score	1.87 (.038)*	1.70 (.079)*	1.16 (.622)*

*Treatment in favor of nabiximols.

be a discernable pattern in the remaining deaths that would raise concern about a link to the study drug."

Discussion

This controlled trial evaluated a novel cannabinoid formulation, nabiximols, using a study design intended to obtain information about its dose response for analgesia and safety in a population with advanced cancer and opioid-refractory pain.

Primary and Secondary Endpoints

The preplanned primary endpoint analysis, a comparison of the proportion of patients in each study group that obtained a 30% reduction in baseline pain, was not statistically significant. However, secondary pain analyses, including the continuous responder analysis and the analysis of change from baseline in mean average pain and worst pain scores, were consistent in showing that nabiximols at lower doses yields significant analgesic effects. Overall, the study supports the conclusion that nabiximols has analgesic efficacy when used as add-on therapy in a population of cancer patients with pain that is poorly responsive to opioids.

In absolute terms, the nabiximols low-dose group achieved a 26% improvement in pain compared with baseline. All changes in pain scores occurred in the absence of any change in regularly scheduled or as-needed opioid consumption. Although the scheduled opioid dose could have been lowered during the study, this was discouraged and the potential for an opioid-sparing effect following the addition of nabiximols therapy could not be fairly assessed in this design.

The study did not find an analgesic effect from the high-dose group and also demonstrated that this dose was not well tolerated. Of the 90 patients randomized to the high-dose group, only 59 (66%) could continue at this dose till the end of the study. In contrast, the rate of AEs leading to withdrawal in the low- and medium-dose groups was comparable to placebo.

Patients receiving the low and medium doses of nabiximols recorded improvement in sleep. Sleep disturbance is very common in advanced cancer[18,28] and this improvement may augment the potential benefit of the drug in this population. In contrast, there were some adverse effects noted on cognitive function and nausea scales of the EORTC QLQ-C30, and additional studies will be needed to assess the extent to which cancer patients in general, or various subgroups of patients, will experience the addition of nabiximols as beneficial in terms of the balance between analgesia and side effects.

Table 5. Summary of Adverse Events

	Number (Percentage) of Patients				
	Nabiximols 1–4 Sprays (N = 91)	Nabiximols 6–10 Sprays (N = 87)	Nabiximols 11–16 Sprays (N = 90)	All Nabiximols (N = 268)	Placebo (N = 91)
Days of exposure	2,899	2,685	2,539	8,123	2,700
Patients with AEs	70 (76.9%)	74 (85.1%)	83 (92.2%)	227 (84.7%)	71 (78%)
Number of AEs	319	352	399	1,070	238
Number of treatment-emergent AEs	270	311	334	915	215
Patients with serious treatment-emergent AEs	34 (37.4%)	18 (20.7%)	27 (30%)	79 (29.5%)	22 (24.2%)
Discontinuations because of AEs	13 (14.3%)	15 (17.2%)	25 (27.8%)	53 (19.8%)	16 (17.6%)

Table 6. Most Common Treatment-Emergent Adverse Events (Reported by ≥5% of Patients)

	Number (Percentage) of Patients				
Description of Event	Nabiximols 1–4 Sprays (N = 91)	Nabiximols 6–10 Sprays (N = 87)	Nabiximols 11–16 Sprays (N = 90)	All Nabiximols (N = 268)	Placebo (N = 91)
Neoplasm progression	24 (26.4%)	11 (12.6%)	12 (13.3%)	47 (17.5%)	13 (14.3%)
Nausea	16 (17.6%)	18 (20.7%)	25 (27.8%)	59 (22.0%)	12 (13.2%)
Dizziness	10 (11%)	21 (24.1%)	20 (22.2%)	51 (19%)	12 (13.2%)
Vomiting	9 (9.9%)	14 (16.1%)	19 (21.1%)	42 (15.7%)	7 (7.7%)
Somnolence	8 (8.8%)	16 (18.4%)	15 (16.7%)	39 (14.6%)	4 (4.4%)
Disorientation	5 (5.5%)	5 (5.7%)	8 (8.9%)	18 (16.7%)	1 (1.1%)
Anorexia	6 (6.6%)	5 (5.7%)	11 (12.2%)	22 (8.2%)	10 (11.0%)
Constipation	4 (4.4%)	10 (11.5%)	6 (6.7%)	20 (7.5%)	7 (7.7%)
Dry mouth	7 (7.7%)	8 (9.2%)	7 (7.8%)	22 (8.2%)	7 (7.7%)
Anemia	6 (6.6%)	5 (5.7%)	8 (8.9%)	19 (7.1%)	4 (4.4%)
Diarrhea	5 (5.5%)	4 (4.6%)	8 (8.9%)	17 (6.3%)	4 (4.4%)
Dysgeusia	1 (1.1%)	7 (8.0%)	3 (3.3%)	11 (4.1%)	2 (2.2%)
Headache	5 (5.5%)	6 (6.9%)	4 (4.4%)	15 (5.6%)	1 (1.%)
Asthenia	6 (6.6%)	7 (8%)	5 (5.6%)	18 (6.7%)	6 (6.6%)
Hallucination	1 (1.1%)	1 (1.1%)	6 (6.7%)	8 (3.0%)	5 (5.5%)
Decreased appetite	4 (4.4%)	5 (5.7%)	2 (2.2%)	11 (4.1%)	2 (2.2%)
Fatigue	4 (4.4%)	4 (4.6%)	5 (5.6%)	13 (4.9%)	4 (4.4%)
Pain	4 (4.4%)	2 (2.3%)	5 (5.6%)	11 (4.1%)	2 (2.2%)
Insomnia	2 (2.2%)	2 (2.3%)	4 (4.4%)	8 (3.0%)	5 (5.%)
Stomatitis	5 (5.5%)	2 (2.3%)	3 (3.3%)	10 (3.7%)	0
Weight decreased	5 (5.5%)	1 (1.1%)	2 (2.2%)	8 (3.0%)	2 (2.2%)

There were no positive treatment effects on questionnaires selected to evaluate pain-related functional interference, constipation, impression of global change, and overall quality of life. The lack of improvement in these measures, even among those groups that experienced reduced pain, may be related to the severity of the disease, the relatively short duration of the study, or limited sensitivity of 1 or more of these questionnaires in this study population. Most patients had advanced illness and multiple problems, and the most likely explanation is that pain relief could not address the array of factors causing functional impairment and suffering. Selection of quality-of-life questionnaires that are sensitive enough to detect treatment differences in this patient population, without producing unacceptable burden, poses a significant challenge for future studies.

Table 7. Serious Adverse Events According to Dose Group by System Organ Class

	Number (Percentage) of Patients				
	Nabiximols 1–4 Sprays (N = 91)	Nabiximols 6–10 Sprays (N = 87)	Nabiximols 11–16 Sprays (N = 90)	All Nabiximols (N = 268)	Placebo (N = 91)
Number of patients with at least 1 SAE	35 (38.5%)	18 (20.7%)	28 (31.1%)	81 (30.2%)	23 (25.3%)
Deaths	25 (27.5%)	14 (16.1%)	17 (18.9%)	56 (20.9%)	16 (17.6%)
Blood disorders	4 (4.4%)	0	0	4 (1.5%)	2 (2.2%)
Cardiac disorders	0	0	0	0	1 (1.1%)
Gastrointestinal disorders	1 (1.1%)	3 (3.4%)	4 (4.4%)	8 (3.0%)	2 (2.2%)
General disorders and administration site conditions	4 (4.4%)	1 (1.1%)	4 (4.4%)	9 (3.4%)	2 (2.2%)
Hepatobiliary disorders	0	1 (1.1%)	1 (1.1%)	2 (.7%)	0
Infections and infestations	4 (4.4%)	5 (5.7%)	2 (2.2%)	11 (4.1%)	2 (2.2%)
Injury, poisoning and procedural complications	1 (1.1%)	1 (1.1%)	0	2 (.7%)	1 (1.1%)
Investigations	0	0	1 (1.1%)	1 (.4%)	0
Metabolism and nutrition disorders	1 (1.1%)	1 (1.1%)	3 (3.3%)	5 (1.9%)	1 (1.1%)
Musculoskeletal & connective tissue disorders	0	0	0	0	1 (1.1%)
Neoplasms, benign, malignant and unspecified	26 (28.6%)	12 (13.8%)	13 (14.4%)	51 (19.0%)	15 (16.5%)
Nervous system disorders	1 (1.1%)	1 (1.1%)	3 (3.3%)	5 (1.9%)	0
Psychiatric disorders	1 (1.1%)	1 (1.1%)	2 (2.2%)	4 (1.5%)	0
Renal and urinary disorders	0	0	4 (4.4%)	4 (1.5%)	1 (1.1%)
Respiratory, thoracic and mediastinal disorders	1 (1.1%)	2 (2.3%)	1 (1.1%)	4 (1.5%)	1 (1.1%)
Vascular disorders	0	0	3 (3.3%)	3 (1.1%)	1 (1.1%)

Safety

The design of this study, which incorporated a forced titration to a given dose range, was intended to explore the dose-response relationships of the various effects produced by the drug. Given the potential for synergy between cannabinoids and opioids, the doses that were found to be safe and efficacious in previous studies could not be assumed appropriate in an opioid-treated, medically ill population. The graded-dose design provided information that will be essential in the design of future efficacy trials. It is not itself an optimal design for characterizing analgesic efficacy and AEs when the drug in question must undergo individualized dose titration to identify the most favorable balance between analgesia and side effects. A randomized study that allows dose titration within a broader range for all patients will be needed to better ascertain response rates and maximal efficacy. This type of study should also evaluate measures of other symptoms and quality of life, and may provide a better test of these nonanalgesic outcomes during add-on nabiximols therapy.

The high death rate in this study confirms that the study population had pain associated with advanced illness. Although the number of deaths because of disease progression was expected in this disease population, the higher incidence of death observed in the low-dose nabiximols group was an unanticipated finding. This finding was not observed in a prior study[9] and both occurrence at lower doses and the lack of consistency in cause of death strongly argues against a causal relationship to nabiximols exposure. Marked variability in death rates also was observed among the placebo dose groups, with the medium-dose group substantially lower than either the low or high-dose groups. Given these observations and the lack of a plausible biological explanation, the association appears to be coincidental. Additional studies in very ill populations warrant continued careful assessment of adverse effects.

Limitations

The present study had some limitations that should be considered in interpreting the data. As noted, the forced dose titration design, which was selected to evaluate dose response, presumably sacrificed the opportunity to gain the most accurate perspective on analgesic efficacy and side effects. A controlled trial that incorporates dose individualization within a large range for all patients will be needed to expand the current findings. A second limitation was imposed by the decision to discourage changes in opioid dosing during the study. Although this minimized the complexity in evaluating analgesic response, it also reduced the ability to discern the potential for an opioid-sparing effect. This may obscure analgesic response if drop-outs that occurred as a result of AEs could have been avoided by lowering the opioid dose. It also prevents an evaluation of the therapeutic index, the balance between analgesia and side effects, which has key importance in the clinical setting. The potential benefit on sleep was an important observation, but the use of a nonvalidated sleep measure precludes any definitive perspective on this outcome.

Conclusions

The finding that nabiximols has analgesic efficacy as add-on therapy for pain from advanced cancer that is poorly responsive to opioid therapy has great potential clinical relevance. Although numerous therapeutic strategies exist, such as opioid rotation, better side effect management, and the use of nonpharmacological approaches, the simplest and most acceptable treatment may be the addition of another drug capable of potentiating or providing additive benefit to the opioid.[2] These drugs, known generically as adjuvant analgesics, are numerous, but the paucity of studies in cancer pain complicates therapeutic decision making.[22] The availability of a novel agent for which there is high quality evidence of efficacy and safety would be an advance.

Based on the results of this dose-ranging study, nabiximols in a manageable dose range may prove to offer benefits to a very ill population with refractory pain. Confirmatory studies are strongly warranted. This study suggests the optimum dose range for the next trial (the design of which should provide stronger evidence of analgesic efficacy), effect on opioid dose, AEs, and the potential impact on other outcomes associated with quality of life in advanced cancer. Confirmation of analgesic efficacy of a cannabinoid as adjunctive therapy for pain related to advanced cancer may provide an opportunity to address a significant clinical challenge.

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