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A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment

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Sativex, a THC/CBD fixed dose combination oromucosal spray, does not have an INN. Nabiximols is the FDA US Adopted Name (USAN)

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Conflicts of interest
M. Serpell, S. Ratcliffe, J. Hovorka, M. Schofield and E. Ehler were all investigators in this study and received investigator fees from GW accordingly for their participation in the study. GW medical writers L. Taylor and H. Lauder undertook the initial compilation and quality control review of the manuscript. Together with the other authors, the target journal was then agreed and all authors reviewed and contributed to the content of the manuscript, and agreed upon the final submitted version. All Intellectual Property Rights arising out of the current clinical study are vest in or exclusively licensed to GW.

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Abstract

Background: Peripheral neuropathic pain (PNP) associated with allodynia poses a significant clinical challenge. The efficacy of Δ^9-tetrahydrocannabinol/cannabidiol (THC/CBD) oromucosal spray, a novel cannabinoid formulation, was investigated in this 15-week randomized, double-blind, placebo-controlled parallel group study.

Methods: In total, 303 patients with PNP associated with allodynia were screened; 128 were randomized to THC/CBD spray and 118 to placebo, in addition to their current analgesic therapy. The co-primary efficacy endpoints were the 30% responder rate in PNP 0–10 numerical rating scale (NRS) score and the mean change from baseline to the end of treatment in this score. Various key secondary measures of pain and functioning were also investigated.

Results: At the 30% responder level, there were statistically significant treatment differences in favour of THC/CBD spray in the full analysis (intention-to-treat) dataset [$p = 0.034$; 95% confidence interval (CI): 1.05–3.70]. There was also a reduction in mean PNP 0–10 NRS scores in both treatment groups that was numerically higher in the THC/CBD spray group, but which failed to reach statistical significance. Secondary measures of sleep quality 0–10 NRS score ($p = 0.0072$) and Subject Global Impression of Change (SGIC) ($p = 0.023$) also demonstrated statistically significant treatment differences in favour of THC/CBD spray treatment.

Conclusions: These findings demonstrate that, in a meaningful proportion of otherwise treatment-resistant patients, clinically important improvements in pain, sleep quality and SGIC of the severity of their condition are obtained with THC/CBD spray. THC/CBD spray was well tolerated and no new safety concerns were identified.

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What's already known about this topic?

- Neuropathic pain is a debilitating form of chronic pain and can be difficult to treat, with only approximately half of sufferers achieving partial relief, often requiring the use of novel analgesics due to the ineffectiveness of conventional pharmacotherapies.
- Cannabinoids, including Δ^9-tetrahydrocannabinol/cannabidiol (THC/CBD) spray, have demonstrated efficacy in addressing this unmet need. A previous randomized controlled trial in neuropathic pain patients demonstrated positive effects in pain and allodynia at 5 weeks.

What does this study add?

- The study demonstrates that THC/CBD spray can provide clinically relevant improvements in pain, sleep quality and patient global impression of the change in their condition in a meaningful proportion of usually treatment-resistant patients.
- This supports the hypothesis that THC/CBD could be a useful candidate for peripheral neuropathic pain treatment, demonstrating efficacy in a few key outcomes over a much longer period of time (15 weeks compared to 5 weeks).

1. Introduction

Neuropathic pain is a chronic, debilitating and widespread condition with an estimated prevalence of over 1% (Backonja and Serra, 2004). Two recent population-based studies in Europe estimated the prevalence of chronic neuropathic pain, or pain with neuropathic characteristics, to be 8% and 7%, respectively (Torrance et al., 2006; Bouhassira et al., 2008). Neuropathic pain can be triggered by a variety of diseases and conditions, but the mechanisms that establish and maintain it are specific to the characteristics of the damage and/or dysfunction of the nervous system. Allodynic pain, characterized as pain evoked by a normally non-nociceptive stimulus (such as temperature), is a subgroup of peripheral neuropathic pain (PNP) and can be very difficult to treat.

A mechanistic approach to neuropathic pain is currently believed to represent the optimal means of symptom management (Jensen et al., 2001; Woolf and Max, 2001). However, there is little clinical proof that this approach is the most effective strategy. Existing therapies for PNP include tricyclic and related antidepressants, anti-epileptic agents and opioids (Attal et al., 2006). However, these therapies may have only a limited effect on PNP, and the side-effect problems associated with each are well known.

The endocannabinoid system modulator, Δ^9-tetrahydrocannabinol (THC)/cannabidiol (CBD) oromucosal spray, is formulated from plant-based extracts prepared from genetically distinct chemotypes of *Cannabis sativa* L. and contains an approximately 1:1 ratio of THC : CBD, plus smaller amounts of other compounds, including minor cannabinoids and terpenes (Russo, 2011). It was recently licensed for use in various European countries for the relief of spasticity in multiple sclerosis (MS) (MHRA Public Assessment Report, 2010), as well as outside the European Union (in Canada, Israel, New Zealand). THC/CBD spray is also licensed for use in Canada for the treatment of central neuropathic pain (CNP) in MS patients.

Cannabinoids are thought to act primarily via specific receptors, designated cannabinoid receptor-1 (CB_1) and cannabinoid receptor-2 (CB_2). CB_1 receptors are predominantly distributed throughout the nervous systems, while CB_2 receptors are primarily located in the periphery, especially the immune system (Howlett et al., 2002).

Cannabinoids are postulated to offer a new therapeutic approach to neuropathic pain treatment. Previous studies using synthetic THC and a synthetic metabolite of THC demonstrated effects in patients on CNP (Svendsen et al., 2004) and PNP associated with allodynia (Karst et al., 2003), respectively. Furthermore, in a previous randomized controlled trial (RCT) (Rog et al., 2005) and in an open-label extension study (Rog et al., 2007), GW has shown that THC/CBD spray has pain relieving effects in neuropathic pain associated with MS and in difficult to treat pain following brachial plexus avulsion (Berman et al., 2004). In addition, a previous 5-week GW study of THC/CBD spray in the treatment of PNP concluded that THC/CBD spray is an effective treatment, which provided a rapid clinically relevant improvement (Nurmikko et al., 2007).

The objectives of this study were to investigate the therapeutic benefits of 15-week THC/CBD spray treatment on PNP associated with allodynia, as well as associated sleep disturbance and patient quality of life.

2. Methods

2.1 Study design

This was a 15-week (1-week baseline and 14-week treatment period), multi-centre, double-blind, randomized, placebo-controlled, parallel group study to evaluate the efficacy of THC/CBD spray in patients with PNP associated with

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allodynia. The study took place at 21 centres in the United Kingdom (UK), seven centres in Czech Republic, six centres in Romania, four centres in Belgium and one centre in Canada. The study was approved by the relevant Institution Review Board or Ethical Committee in each country and was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. All patients provided written informed consent to take part in the study.

All visits took place at study centres. Following eligibility screening, patients completed a 7-day baseline period. Patients were then assessed, randomized and received dose introduction. Visits occurred at the end of weeks 2, 6, 10 and at the end of the study (treatment week 14) or earlier if they withdrew. A follow-up visit occurred 28 days after study completion or withdrawal. Patients were then given the opportunity to enrol in an open-label extension study. Results from the open-label extension study will not be presented in this report.

At each visit, the following information was recorded: adverse events (AEs), vital signs, intoxication 0–10 numerical rating scale (NRS), sleep quality 0–10 NRS, PNP 0–10 NRS, neuropathic pain scale (NPS), use of rescue analgesia, any changes in current medical conditions, dose of regular maintenance analgesic, changes in concomitant medication, current dose of study medication and medication compliance. Clinical laboratory sampling (haematology, biochemistry and urinalysis) was carried out at screening and at the end of treatment.

2.2 Inclusion and exclusion criteria

2.2.1 Inclusion criteria

Eligible patients were aged 18 or older, had mechanical allodynia within the territory of the affected nerve(s) (confirmed by either a positive response to stroking the allodynic area with a SENSELAB™ Brush 05 (Somedic AB, Hörby, Sweden) or to force applied by a 5.07 g Semmes-Weinstein monofilament), at least a 6-month history of PNP, and were receiving the appropriate treatment for their PNP. Eligible patients had at least one of the following underlying conditions, which caused their PNP: post-herpetic neuralgia, peripheral neuropathy, focal nerve lesion, radiculopathy or Complex Regional Pain Syndrome (CRPS) type 2. Patients also had a sum score of at least 24 on a pain 0–10 NRS for more than 6 days (baseline days 2–7) during the baseline period (average 0–10 NRS score of 4/10), and pain that was not wholly relieved by their current therapy. In addition, their analgesic regimen was stable for at least 2 weeks preceding study entry and they were willing for the responsible authorities (i.e., primary care consultant or physician) to be notified of their participation in the study.

2.2.2 Exclusion criteria

Patients with severe pain from other concomitant conditions were excluded, as were those with a history of significant psychiatric, renal, hepatic, cardiovascular or convulsive disorders, or with a known hypersensitivity to the study medication. Those with CRPS type 1, cancer-related PNP or pain resulting from diabetes mellitus were excluded. Patients receiving a prohibited medication [including cannabis or cannabinoid-based medications (in the last year), any analgesics taken on a 'PRN' (when required) basis, the introduction of any new analgesic medication, or any alteration to the dosage of the patient's concomitant analgesic medication (other than the rescue analgesia provided), or all paracetamol-containing medications (stopped on the day the patient entered the baseline period)], who were unwilling to abstain for the study duration were also excluded, as were those with a known history of alcohol or substance abuse. Women of child-bearing potential or their partners were excluded unless willing to ensure effective contraception was used throughout the study, as were those who had received an investigational medicinal product within 12 weeks of screening. Pregnant or lactating women and those planning a pregnancy were excluded. Patients with any physical abnormality at screening (i.e., any abnormalities that, in the opinion of the investigator, would prevent the patient from safely participating in the study), or those intending to travel or donate blood during the study were also ineligible to take part.

2.3 Study medication and procedures

A pump action oromucosal spray was used to deliver study medication. Each 100 μL spray of THC/CBD delivered 2.7 mg of THC and 2.5 mg of CBD to the oral mucosa, and each spray of placebo delivered the excipients plus colorants. Both THC/CBD spray and placebo contained peppermint oil to blind the smell and taste. Patients self-administered the medication to their optimal dose, but were restricted to a maximum of eight sprays in a 3-h period up to a maximum of 24 sprays per 24-h period. Initially, patients began at a maximum of one spray per 4-h period. Thereafter patients were advised to self-titrate their medication to symptom relief or maximum dose, but increases were limited to a maximum of 50% of the previous day's dose.

2.3.1 Concomitant medications

As would be expected in this group of patients, many were receiving concomitant medications for analgesia and were allowed to continue their concomitant analgesic medication, with the exception of paracetamol (acetaminophen), provided that a stable dose was maintained throughout the study. Patients were not permitted to take analgesics on a 'PRN' (when required) basis, and the introduction of any new analgesic medication or any alteration to the dosage of the patients' concomitant analgesic medication (other than the rescue analgesia provided) was prohibited during the study. The rescue analgesia provided contained paracetamol Ph Eur 500 mg. The maximum single dose was two 500 mg tablets, and the maximum total daily dose was 4 g (i.e., 8

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tablets per day). A single dose was not to be taken more frequently than every 4 h, with no more than four doses in any 24-h period.

2.4 Study endpoints

2.4.1 Primary efficacy endpoints

In this study, a 0–10 NRS was used as the primary measure of pain severity. The efficacy endpoints for analysis were the proportion of patients showing a 30% or more improvement from baseline to the end of treatment in PNP 0–10 NRS score, and the mean change in PNP 0–10 NRS score from baseline to the end of treatment. End of treatment PNP 0–10 NRS scores were the average of all scores during the last 7 days of the evaluable treatment period.

The PNP 0–10 NRS was recorded daily by patients in their diary books. Each patient was instructed to complete their PNP 0–10 NRS score by reviewing their day's pain at the end of every day. Patients were asked, 'On a scale of "0 to 10", please indicate the average level of your nerve pain over the last 24 h', with the anchors: 0 = 'no pain', 10 = 'worst possible pain'. The assessment reviewed the entire day's pain, and therefore, the perception of pain was less likely to be influenced directly by sleep, compared with an assessment made on waking. Patients were instructed to relate 'no pain' to the time prior to their onset of their PNP associated with allodynia.

2.4.2 Secondary efficacy endpoints

Secondary endpoints included the mean changes from baseline to the end of treatment in the following scores: NPS, sleep quality 0–10 NRS, Subject Global Impression of Change (SGIC), Brief Pain Inventory (short form) (BPI-SF), dynamic and punctate allodynia tests, quality of life (EQ-5D) health questionnaire, as well as the proportion of patients showing a 50% or more improvement in PNP 0–10 NRS score, and the use of rescue analgesia.

2.4.2.1 NPS

The NPS (neuropathic pain scale PDF) was collected weekly in the patient diaries during the whole length of the study. The variable for analysis was the change in mean NPS score from baseline (mean of two assessments during the baseline period) to the end of the study (mean of last two assessments during the evaluable period).

The NPS consists of 10 individual items. Nine of these provide a total of ten 0–10 NRS responses and there is a multi-part free text question. The NPS score to be used for the analysis was the sum of the ten 0–10 NRS responses. If up to three individual items were missing, then an NPS score was imputed by multiplying the mean of the completed items by 10. If more than three individual items were missing, then the whole score was missing.

2.4.2.2 Sleep quality 0–10 NRS

Sleep quality was assessed at all study visits on a 0–10 NRS, with the main variable for analysis being the change from baseline to the end of treatment in sleep quality 0–10 NRS score. The sleep quality 0–10 NRS was completed at the same time each day, i.e., bedtime in the evening. The patient was asked 'on a scale of "0 to 10", please indicate how your pain disrupted your sleep last night', with the anchors: 0 = 'did not disrupt sleep' and 10 = 'completely disrupted (unable to sleep at all)'.

2.4.2.3 SGIC

At baseline, patients wrote a brief description of their pain caused by peripheral neuropathy, which was used at the end of treatment to aid their memory regarding their symptoms at the start of the study. The SGIC was completed at the end of treatment. A 7-point Likert-type scale was used to evaluate the patients' perception of their condition, and patients were asked, 'Please assess the status of your pain due to peripheral neuropathy since entry into the study using the scale below', with the anchors: 'very much improved', 'much improved', 'slightly improved', 'no change', 'slightly worse', 'much worse' or 'very much worse'.

2.4.2.4 BPI-SF

The BPI-SF (Cleeland and Ryan, 1994) was performed twice, once at baseline and once at the end of treatment, with the change in score between these time points being the variable for analysis. The BPI-SF consists of nine questions, each of which consists of a single response apart from question 9, which is sub-divided into seven parts (9A–9G). Questions 3–6 ask patients to rate pain on a 0–10 scale over the prior week (where 0 = 'no pain' and 10 = 'pain as bad as you can imagine'). Severity is measured as worst pain, least pain, average pain and pain right now. The severity composite score was calculated as the arithmetic mean of the four severity items (range 0–10). The minimum value is zero and maximum is 10.

The BPI-SF also records the degree to which pain interferes with activities on a 0–10 scale (where 0 = 'does not interfere at all' and 10 = 'pain completely interferes with activity'). As such, a higher score represents a poorer outcome.

Two composite scores were calculated from the BPI-SF:
(1) The pain severity composite score: the arithmetic mean of the four pain scores (questions 3–6) and represents the pain intensity.
(2) The pain interference composite score: the arithmetic mean of the seven interference items (questions 9A–9G) and represents the effect of pain.

2.4.2.5 Dynamic allodynia test

The dynamic allodynia test was performed twice, once at baseline and once at the end of treatment, with the change in score between these time points being the variable for analy-

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sis. At each time point, dynamic allodynia was assessed by stroking the skin over the affected area five times with a SENSELAB Brush 05, designed specifically for sensory testing at 5-s intervals, and recording the pain severity on a 0–10 NRS, where 0 = 'no pain' and 10 = 'most pain imaginable'. All strokes were of the same length, minimum 2 cm. The mean of the five scores for the identified allodynic area only was calculated to define the dynamic allodynia pain score.

2.4.2.6 Punctate allodynia test

The punctate allodynia test was performed twice, once at baseline and once at the end of treatment, with the change in score between these time points being the variable for analysis. Punctate allodynia was measured using an in-house built pressure algometer comprising a strain gauge connected to a metal filament with a diameter of 1 mm and blunt tip at baseline and end of study. The filament was manually directed against the skin at an angle of 90° and a steadily increasing pressure was applied until the patient verbally indicated that they perceived pain (punctate pressure pain threshold). Patients were asked to verbally rate the intensity of the pain elicited, choosing a number between 0 = 'no pain' and 10 = 'most intense pain imaginable'. The average of the ascending pain threshold forces, as available, for the identified allodynic area only was calculated to define the punctate allodynia pain threshold force.

2.4.2.7 EQ-5D questionnaire

The EQ-5D questionnaire (The Euroqol Group, 1990) was completed twice during the study, once at baseline and once at the end of treatment.

The EQ-5D questionnaire provided two outcomes:

(1) A weighted health state index visual analogue scale (VAS).

(2) A self-rated health status VAS.

The self-rated health status VAS anchors were: 0 = 'worst health state imaginable' to 100 = 'best health state imaginable'. The weighted health state index used the same VAS as above but was calculated for each assessment without imputation to account for missing values, i.e., if one or more individual items were missing, then the whole index was missing.

The change from baseline to the end of treatment was calculated for both VASs.

2.4.2.8 Use of rescue analgesia

Use of breakthrough medication was recorded daily during the study as the number of paracetamol tablets taken. The change in mean daily quantities of tablets used was calculated from baseline to the last 7 days of treatment.

2.4.3 Safety endpoints

The safety endpoints were the incidence of AEs and serious adverse events (SAEs), clinical laboratory sampling pre- and post-treatment, vital signs, oral examination and intoxication 0–10 NRS.

2.4.4 Sample size

Based upon previous GW studies, it was believed that this study would result in a difference in the primary endpoint between THC/CBD spray and placebo patients of at least 0.9 points on the PNP 0–10 NRS. Also based on previous GW studies and the literature, it was estimated that the standard deviation of the changes from baseline in the primary endpoint would be approximately 2.1 points (Rowbotham et al., 1998; Rice et al., 2001; Serpell and Neuropathic Pain Study Group, 2002; Boureau et al., 2003). Taking this into account, for a significance level of 5% and 80% power, we would need a total of 174 evaluable patients (87 in each group) to detect a difference of 0.9 points in the PNP 0–10 NRS. Allowing for 20% of randomized patients to be unevaluable, then 218 patients (109 in each group) would need to be randomized.

2.5 Method of assigning patients to treatment groups and blinding

Patients were randomized to receive either THC/CBD spray or placebo. Randomization was carried out using a predetermined computer-generated randomization code, produced by the GW Biometrics Department, in which treatment allocation was made using permuted blocks of four. Study medication was pre-packed by the GW Clinical Trial Supplies Department and dispatched to the investigator centres labelled with patient numbers. The randomization scheme involved patient numbers being assigned sequentially by the investigator staff.

Study medication was provided in 5.5-mL type I amber glass vials labelled with the GW name, study code, patient number, visit number and the expiry date. The investigator staff, pharmacy and GW Clinical Department held sealed code break envelopes for each patient. Since THC/CBD spray is a plant-based extract in alcoholic solution with a distinctive smell, taste and colour, both THC/CBD spray and placebo contained peppermint oil to blind the smell and taste. The placebo also contained quinoline and sunset yellow, to match the colour of the plant extract. As such, participants, investigators are caregivers were all blinded to the treatment allocation.

2.6 Statistical methods

All randomized patients who received at least one dose of test treatment and had on-treatment efficacy data were included in the intention-to-treat (ITT) analysis set. The per protocol (PP) analysis set included those with evaluable data for the primary parameter with no protocol deviations, which were considered to affect the comparison between treatments for this endpoint. All summaries and statistical analyses were performed using SAS Version 9.1 (SAS Insti-

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tute Inc., Cary, NC, USA). Statistical comparisons of efficacy data between treatments used two-sided statistical tests at the 5% significance level. PNP 0–10 NRS scores were evaluated by analysis of covariance (ANCOVA), with baseline values as covariate and treatment group and centre group as main effect. These tests were performed at the 10% significance level as a possible indicator of an interactive effect. An additional analysis was performed on the PNP 0–10 NRS dataset to assess the time course of the treatment effect using repeated measures. A multivariate linear model was used with a separate unstructured covariance matrix in each treatment arm. The mean (fixed effects structure) incorporated full treatment-by-(categorical) time interaction. Baseline was included as a covariate, together with baseline-by-time interaction. Grouped centre was included as a categorical covariate. The fitted model was also used to produce a final time point comparison.

Changes from baseline to the end of treatment were compared between treatment groups using ANCOVA for the following secondary endpoints: NPS, dynamic allodynia pain score, punctate allodynia pain score, BPI-SF, sleep quality 0–10 NRS and EQ-5D. Models included treatment and centre group as factors and baseline mean usage as a covariate.

The change from baseline in mean daily quantity of rescue analgesia usage was analysed in a fashion similar to the PNP 0–10 NRS.

In the SGIC outcome, the two treatment groups were compared using ordinal logistic regression and the proportional odds model, incorporating centre group.

2.7 Amendments during trial

The following inclusion criterion was removed: 'Subject has at least moderate PNP, which is defined as the total of the two NPS scores before randomization being at least 80'. After ethics approval had been granted for the study, the Committee for Medicinal Products for Human Use (CHMP) Guideline on Clinical Investigation of Medicinal Products Intended for the Treatment of Neuropathic Pain were finalized and issued (CPMP guideline, 2004). The CHMP guidance notes clearly recommended that the 0–10 NRS should be used as the primary efficacy endpoint. Therefore, to have an entry criterion of the two NPS scores before randomization being at least 80 in addition to the minimum 0–10 NRS pain scores was considered futile. The NPS was still collected as a secondary outcome measure and analysed and reported accordingly.

3. Results

The study took place between 27 September 2005 and 18 October 2006. In total, 303 patients were recruited and 246 were randomized and analysed at 39 study centres. Of these, 128 received THC/CBD spray, 118 received placebo and 57 were withdrawn before randomization. A total of 173 patients completed the study, 21 ceased treatment but remained in the study, and 52 withdrew. Six patients (one taking placebo and five taking THC/CBD spray) were not included in the analysis as they had no on-treatment efficacy data. A summary of the flow of the trial can be found in Fig. 1. The mean duration of the underlying neuropathic condition in these patients was similar between treatment groups at approximately 6 years with the minima and maxima also being similar at 0.6–38.1 years for THC/CBD spray and 0.4–39.3 years for placebo groups, respectively. The duration of their treatment-resistant neuropathic pain was also similar and no notable differences in the proportions of patients with each type of underlying condition were seen between treatment groups, the most common of which was focal nerve lesions for both groups. These and other study population demographics are displayed in Table 1. Overall, the mean daily dose of THC/CBD spray was 8.9 sprays and for placebo was 14.2 sprays, and the median duration of treatment was 78.2 days for THC/CBD spray and 86.4 days for placebo.

3.1 Concomitant medication

The majority of patients (90% overall) continued to take analgesics during the study. The most commonly reported classes of analgesic were non-selective monoamine reuptake inhibitors (tricyclic antidepressants) taken by 26% of patients, anti-epileptics (pregabalin) taken by 20% of patients and other anti-epileptics (gabapentin) taken by 23% of patients. In addition, 19% and 18% of patients, respectively, took natural opium alkaloids (such as dihydrocodeine) and other opioids (mostly tramadol). The most commonly reported classes of non-analgesic concomitant medication were proton pump inhibitors (18%), HMG Co-A reductase inhibitors (statins, 15%), angiotensin-converting enzyme inhibitors (14%) and beta blocking agents (13%).

3.2 Primary endpoint: 30% responder analysis and change from baseline to the end of treatment in PNP 0–10 NRS

A total of 34 patients (28%) receiving THC/CBD spray were classified as responders at the 30% level compared with 19 patients (16%) on placebo. Responder analysis at this level showed a statistically significant treatment difference in the evaluable period for the ITT population with an odds ratio of 1.97 ($p = 0.034$; 95% CI: 1.05–3.70), in favour of THC/CBD spray treatment (Table 2). This finding was supported by the PP analysis set, in which 27 (36%) of patients in the THC/CBD spray treatment group achieved at least a

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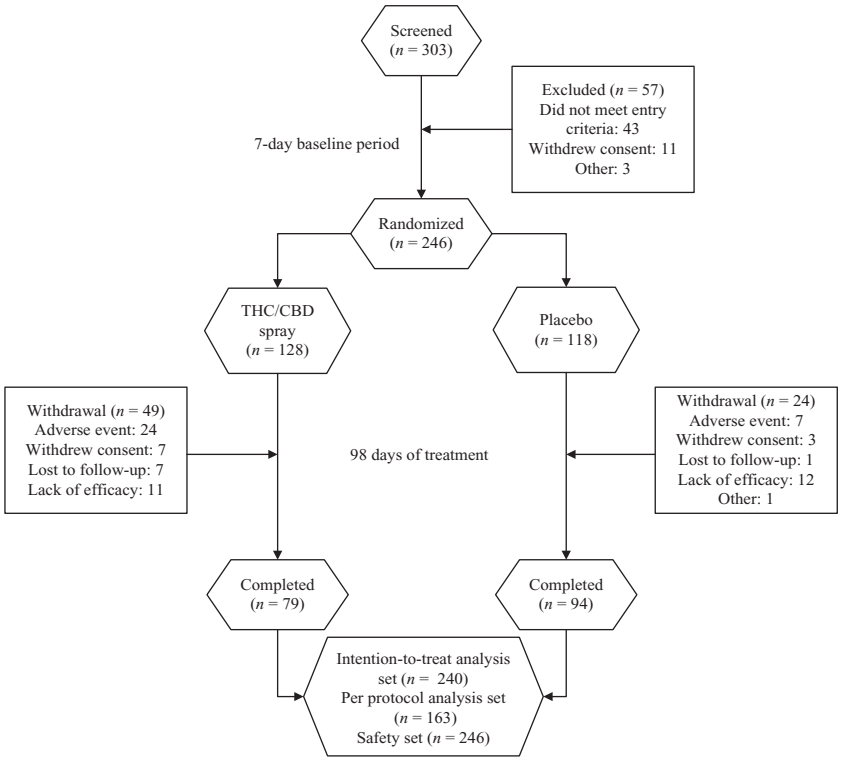

Figure 1 Breakdown of patients enrolled in the study.

30% improvement in 0–10 NRS pain scores compared with 18 (20%) in the placebo treatment group, with an odds ratio of 2.27 ($p = 0.021$; 95% CI: 1.12–4.57) (Table 2). For 30% responders, the proportion of responders was observed to increase much more quickly in relation to the dose of THC/CBD spray compared with placebo, as illustrated in Fig. 2. At a point of around 14–15 sprays per day, the response rate in

Table 1 Demographics and baseline characteristics for all patients who took part in the study.

	THC/CBD spray (*n* = 128)	Placebo (*n* = 118)	Total (*n* = 246)
	No. of patients (%)		
Gender			
Male	43 (34)	53 (45)	96 (39)
Female	85 (66)	65 (55)	150 (61)
Ethnic origin			
White/Caucasian	127 (99)	116 (98)	243 (99)
Black/African American	0	2 (2)	2 (1)
Other	1 (1)	0	1 (< 0.5)
Previous cannabis use in the last year	13 (10)	12 (10)	25 (10)
Type of underlying condition causing neuropathic pain			
Post-herpetic neuralgia	34 (27)	30 (25)	64 (26)
Peripheral neuropathy	35 (27)	25 (21)	60 (24)
Focal nerve lesion	44 (34)	52 (44)	96 (39)
Complex regional pain syndrome-II	17 (13)	14 (12)	31 (13)
	Mean (SD)		
Age (years)	57.6 (14.4)	57.0 (14.1)	57.3 (14.2)
Body mass index (kg/m^2)	28.4 (6.5)	27.3 (4. 9)	27.9 (5.8)
Duration of neuropathic condition (years)	6.3 (6.7)	6.3 (6.4)	6.3 (6.6)
Duration of peripheral neuropathic condition (years)	5.7 (6.3)	5.2 (5.4)	5.5 (5.9)

CBD, cannabidiol; THC, Δ^9-tetrahydrocannabinol.

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Table 2 Summary of the analysis of all primary and secondary efficacy endpoints (ITT and PP analysis sets). Treatment differences between THC/CBD spray and placebo are presented using change from baseline to the end of treatment data for each endpoint, unless otherwise stated.

Endpoint	ITT analysis set			PP analysis set		
Primary endpoints						
	Odds ratio	95% CI	*p*-value	Odds ratio	95% CI	*p*-value
30% responder analysis (PNP 0–10 NRS)	1.970	1.049 to 3.702	0.034	2.266	1.124 to 4.568	0.021
	Treatment difference (SE)	95% CI	*p*-value	Treatment difference (SE)	95% CI	*p*-value
PNP 0–10 NRS	–0.34 (0.230)	–0.79 to 0.11	0.139	–0.48 (0.303)	–1.08 to 0.12	0.116
Secondary endpoints						
	Treatment difference (SE)	95% CI	*p*-value	Treatment difference (SE)	95% CI	*p*-value
NPS	–2.86 (2.211)	–7.22 to 1.50	0.198	–5.26 (2.873)	–10.94 to 0.41	0.069
Sleep quality 0–10 NRS	–0.83 (0.306)	–1.43 to –0.23	0.007	–0.91 (0.369)	–1.63 to –0.18	0.015
BPI-SF (pain severity composite score)	–0.25 (0.236)	–0.72 to 0.21	0.288	–0.27 (0.291)	–0.85 to 0.30	0.349
BPI-SF (average pain)	–0.34 (0.237)	–0.81 to 0.12	0.148	–0.47 (0.299)	–1.06 to 0.13	0.122
BPI-SF (worst pain)	–0.30 (0.265)	–0.82 to 0.22	0.255	–0.39 (0.322)	–1.02 to 0.25	0.234
BPI-SF (pain interference composite score)	–0.32 (0.241)	–0.80 to 0.15	0.183	–0.39 (0.304)	–0.99 to 0.21	0.204
Dynamic allodynia test	0.08 (0.305)	–0.52 to 0.68	0.795	–0.27 (0.359)	–0.98 to 0.44	0.460
Punctate allodynia test	–0.14 (0.118)	–0.37 to 0.09	0.233	–0.06 (0.150)	–0.35 to 0.24	0.701
EQ-5D (weighted health status index VAS)	–0.01 (0.024)	–0.06 to 0.04	0.617	–	–	–
EQ-5D (self-rated health status VAS)	–0.75 (2.459)	–5.60 to 4.09	0.760	–	–	–
Use of rescue analgesia	–0.38 (0.237)	–0.85 to 0.09	0.112	0.40 (0.316)	–1.02 to 0.23	0.211
	Odds ratio	95% CI	*p*-value	Odds ratio	95% CI	*p*-value
50% responder analysis (PNP 0–10 NRS)	1.699	0.645 to 4.476	0.280	2.045	0.750 to 5.576	0.157
SGIC (end of treatment only)	1.762	1.080 to 2.876	0.023	2.988	1.661 to 5.378	0.0003

BPI-SF, Brief Pain Inventory (short form); CBD, cannabidiol; CI, confidence interval; ITT, intention-to-treat; NRS, numerical rating scale; PNP, peripheral neuropathic pain; PP, per protocol; SGIC, Subject Global Impression of Change; THC, Δ^9-tetrahydrocannabinol; VAS, visual analogue scale.

patients receiving THC/CBD spray slowed, while for those taking placebo, the proportion of responders was still increasing maximally.

In the co-primary endpoint of change from baseline to the end of treatment in PNP 0–10 NRS score, for the ITT and PP datasets, the adjusted mean reduction in PNP 0–10 NRS score gave respective estimated treatment differences of –0.34 points ($p = 0.14$; 95% CI: –0.79 to 0.11 points) and –0.48 points ($p = 0.12$; 95% CI: –1.08 to 0.12 points), in favour of a benefit with

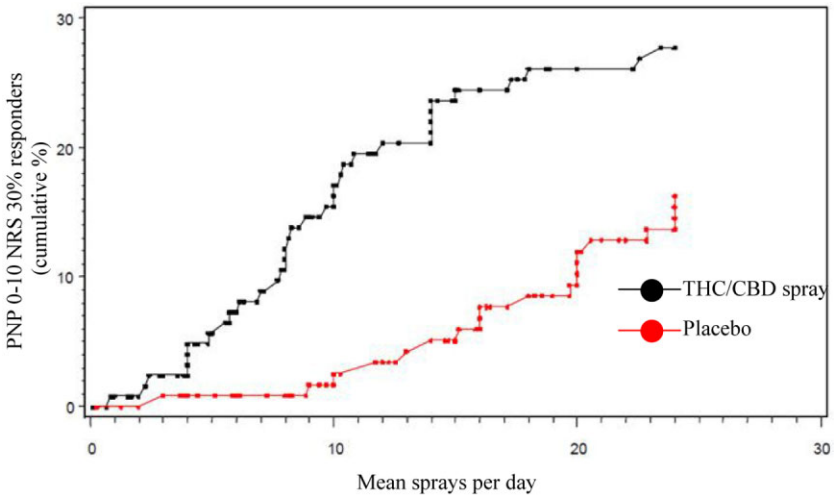

Figure 2 Cumulative percentage of responders at the 30% level by mean sprays.

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Table 3 Sleep quality ratings by study visit, ITT and PP datasets.

	Adjusted mean change from baseline			
	THC/CBD spray (n = 122)	Placebo (n = 117)	Treatment difference (THC/CBD spray vs. placebo)	Lower and upper limits 95% CI
Time point	ITT			
Visit 3 (day 15)	–1.44	–0.73	–0.70	–1.22, –0.19
Visit 4 (day 43)	–1.45	–0.74	–0.71	–1.31, –0.11
Visit 5 (day 71)	–1.39	–0.66	–0.74	–1.34, –0.13
Visit 6 (day 99)	–1.47	–0.69	–0.78	–1.36, –0.21
Final visit (day 127)	–1.57	–0.74	–0.83	–1.43, –0.23
	PP			
	(n = 73)	(n = 89)		
Visit 3 (day 15)	–1.46	–0.81	–0.65	–1.30, –0.01
Visit 4 (day 43)	–1.62	–0.83	–0.78	–1.58, 0.01
Visit 5 (day 71)	–1.52	–0.71	–0.81	–1.58, –0.03
Visit 6 (day 99)	–1.49	–0.58	–0.91	–1.63, –0.18
Final visit (day 127)	–1.49	–0.58	–0.91	–1.63, –0.18

CBD, cannabidiol; CI, confidence interval; ITT, intention-to-treat; PP, per protocol; THC, Δ^9-tetrahydrocannabinol.

THC/CBD spray treatment. However, these failed to reach statistical significance.

3.3 Secondary efficacy analysis

At the 50% responder level in the PNP 0–10 NRS score analysis, the treatment difference was also in favour of the THC/CBD spray treatment group in both the ITT and the PP populations, but did not reach statistical significance in either population (Table 2).

For the ITT complete period, the adjusted mean sleep quality 0–10 NRS score decreased (improved) by 1.57 points from a mean baseline score of 5.4 points in the THC/CBD spray group, compared with an adjusted decrease of 0.74 points from a baseline of 5.8 points in the placebo group. The estimated treatment difference was −0.83 points, in favour of THC/CBD spray, a highly statistically significant result compared with placebo ($p = 0.0072$; 95% CI: −1.43 to −0.23 points) (Table 3). In the PP population, the treatment difference was slightly greater, in favour of THC/CBD spray, and was also statistically significant compared with placebo (−0.91 points, $p = 0.015$; 95% CI: −1.63 to −0.18 points) (Table 3).

In the secondary efficacy analysis of SGIC, there was a statistically significant treatment difference in favour of THC/CBD spray in the ITT dataset, compared with placebo (odds ratio: 1.76; $p = 0.023$; 95% CI: 1.08–2.88) that was mirrored in the PP population, with the odds ratio in favour of THC/CBD spray increasing to 2.99 compared with placebo ($p = 0.0003$; 95% CI: 1.66, 5.38). The proportion of patients selecting each category is presented in Fig. 3.

Decreases (improvements) in favour of the THC/CBD spray group were also observed in the following parameters: NPS total score, mean number of tablets of rescue medication administered, BPI-SF scores (pain severity composite score, average pain, worst pain and pain interference composite score) and EQ-5D questionnaire scores (both weighted health status index VAS and self-rated health status VAS). These results applied to both ITT and PP population analysis sets, but none reached statistical significance (Table 2). The dynamic allodynia test score increased (improved) in the ITT analysis set but was not in favour of active treatment in the PP analysis set (Table 2).

Interestingly, there was an apparent treatment by centre interaction in the changes from baseline to the end of treatment in sleep quality 0–10 NRS ($p = 0.016$) and BPI-SF scores ($p = 0.079$) (in the domain of 'pain interference composite'), with an apparent treatment effect in the UK but not elsewhere (data not shown).

3.4 Safety and tolerability

All AEs experienced by patients with an incidence of 3% or greater during this study are displayed in Table 4. The most common system organ classes (SOCs) affected for treatment-related AEs were 'nervous system disorders', 'gastrointestinal disorders', 'general disorders and administration site conditions', 'infections and infestations' and 'psychiatric disorders'. 'Psychiatric disorders' were experienced by 36 (28%) patients receiving THC/CBD spray versus only 11 (9%) receiving placebo. By preferred term, dissociation [nine (7%) THC/CBD spray patients affected vs.

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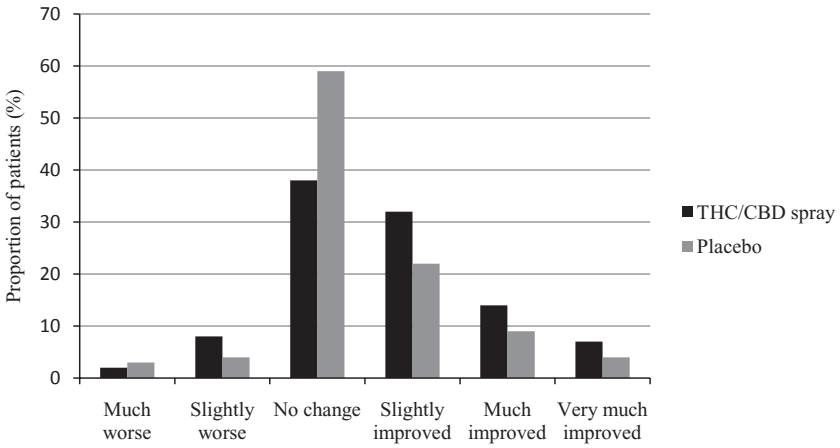

Figure 3 Subject global impression of change, intention-to-treat complete period.

no placebo patients] and disorientation [eight (6%) THC/CBD spray patients affected vs. no placebo patients] were the most commonly reported AEs in this SOC (Table 4). Additionally, other SOCs were more commonly affected in the THC/CBD spray versus placebo arms, notably 'nervous system disorders', 'gastrointestinal disorders' and 'general disorders and administration site conditions' (Table 4).

The majority of treatment-emergent AEs were mild to moderate in severity across both treatment groups. Ten patients (8%) receiving THC/CBD spray experienced SAEs, none of which was considered to be treatment-related. Six patients (5%) receiving placebo experienced a treatment-emergent SAE, one of which was considered related to treatment. A total of 33 patients stopped receiving study medication due to AEs, 25 in the THC/CBD spray arm and 8 in the placebo group. No obvious trends were shown for biochemistry, haematology or urinalysis, and no mean changes in blood pressure and pulse rate were observed from baseline to final visit. Furthermore, no patients died during the course of this study.

4. Discussion

Neuropathic pain is one of the most difficult types of pain to treat (The Committee for Medicinal Products for Human Use (CHMP), 2004), with fewer than half of treated patients receiving meaningful benefit from any pharmacological drug (Attal et al., 2006). The current study patients represented an especially resistant treatment group as they had not responded adequately to existing therapies, had a mean pain 0–10 NRS score of 4 or above, despite the majority currently taking analgesics for their neuropathic pain, and had a median duration of neuropathic pain of more than 3 years. In the face of such prolonged neuropathic pain, a new therapy faces enormous challenges to modify significantly the changes established within the nervous system. Despite these limiting factors, this study confirms the results previously reported, showing THC/CBD spray to produce a clinically relevant improvement (30% or more) in mean daily pain in a significantly greater proportion of patients than placebo when administered in addition to existing medication (Nurmikko et al., 2007). Furthermore, since the evidence base is considered to be poor for medicines currently licensed for the treatment of evoked neuropathic phenomena, these findings suggest that THC/CBD spray is a promising new candidate for treating mixed neuropathic pain characterized by allodynia (Rowbotham et al., 1998). An additional advantage of THC/CBD oromucosal spray is the simple handling and fast action of the medicament.

A greater than 30% improvement in pain intensity, considered to signify a clinically meaningful improvement (Rasmussen et al., 2004), was reported by 28% of patients receiving THC/CBD spray compared with 16% of patients taking placebo. This finding was statistically significant in favour of THC/CBD spray and, considering the patient population in the study, is encouraging. The co-primary analysis of the mean change from baseline to the end of treatment in PNP 0–10 NRS score also showed a treatment difference in favour of THC/CBD spray, but this did not reach statistical significance.

The importance of sleep in chronic pain states has been well established (Casarett et al., 2001; Turk and Dworkin, 2004), and improved sleep is considered a significant treatment objective by patients (Dworkin et al., 2005), especially as neuropathic pain tends to be worse at night (Stacey et al., 2010). Here, we demonstrate a statistically significant improvement in sleep with THC/CBD spray treatment, a finding that sup-

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Table 4 Number of patients with at least one all-causality or treatment-related AE with an incidence of 3% or greater by primary system organ class and preferred term (as medically encoded using the Medical Dictionary for Regulatory Activities [MedDRA] version 8.1).

	All-causality		Treatment-related	
System organ class Preferred term	THC/CBD spray (*n* = 128) No. of patients (%)	Placebo (*n* = 118)	THC/CBD spray (*n* = 128) No. of patients (%)	Placebo (*n* = 118)
Total subjects with at least one AE	109 (85)	83 (70)	97 (76)	56 (47)
Nervous system disorders	79 (62)	34 (29)	73 (57)	20 (17)
Dizziness	52 (41)	12 (10)	50 (39)	11 (9)
Dysgeusia	14 (11)	2 (2)	14 (11)	2 (2)
Headache	13 (10)	9 (8)	8 (6)	7 (6)
Disturbance in attention	8 (6)	2 (2)	8 (6)	1 (1)
Neuropathy peripheral	6 (5)	4 (3)	3 (2)	0
Tremor	6 (5)	0	4 (3)	0
Somnolence	5 (4)	2 (2)	5 (4)	2 (2)
Balance disorder	4 (3)	2 (2)	4 (3)	2 (2)
Memory impairment	4 (3)	2 (2)	4 (3)	2 (2)
Sedation	4 (3)	0	4 (3)	0
Gastrointestinal disorders	60 (47)	43 (36)	48 (38)	30 (25)
Nausea	23 (18)	14 (12)	22 (17)	9 (8)
Vomiting	13 (10)	7 (6)	6 (5)	3 (3)
Diarrhoea	12 (9)	6 (5)	8 (6)	2 (2)
Dry mouth	11 (9)	4 (3)	11 (9)	4 (3)
Abdominal pain upper	6 (5)	1 (1)	4 (3)	0
Dyspepsia	6 (5)	4 (3)	1 (1)	3 (3)
Constipation	4 (3)	2 (2)	2 (2)	0
Mouth ulceration	4 (3)	6 (5)	4 (3)	6 (5)
Oral pain	4 (3)	3 (3)	4 (3)	3 (3)
General disorders and administration site conditions	45 (35)	30 (25)	38 (30)	23 (19)
Fatigue	20 (16)	8 (7)	19 (15)	5 (4)
Feeling drunk	8 (6)	3 (3)	8 (6)	3 (3)
Application site pain	7 (5)	2 (2)	7 (5)	2 (2)
Psychiatric disorders	36 (28)	11 (9)	30 (23)	4 (3)
Dissociation	9 (7)	0	9 (7)	0
Disorientation	8 (6)	0	8 (6)	0
Depression	6 (5)	0	3 (2)	0
Anxiety	4 (3)	1 (1)	3 (2)	1 (1)
Panic attack	4 (3)	1 (1)	3 (2)	0
Infections and infestations	35 (27)	26 (22)	1 (1)	3 (3)
Nasopharyngitis	9 (7)	8 (7)	1 (1)	1 (1)
Gastroenteritis	4 (3)	1 (1)	0	0
Lower Respiratory Tract Infection	4 (3)	3 (3)	0	0
Metabolism and nutrition disorders	15 (12)	6 (5)	10 (8)	5 (4)
Increased appetite	6 (5)	1 (1)	6 (5)	1 (1)
Anorexia	4 (3)	1 (1)	1 (1)	1 (1)
Respiratory, thoracic and mediastinal disorders	15 (12)	16 (14)	7 (5)	5 (4)
Pharyngolaryngeal pain	7 (5)	5 (4)	2 (2)	5 (4)
Dyspnoea	4 (3)	3 (3)	1 (1)	0
Musculoskeletal and connective tissue disorders	11 (9)	8 (7)	2 (2)	1 (1)
Injury, poisoning and procedural complications	9 (7)	6 (5)	2 (2)	0
Skin and subcutaneous tissue disorders	9 (7)	9 (8)	2 (2)	2 (2)
Rash	5 (4)	4 (3)	1 (1)	0
Eye disorders	7 (5)	6 (5)	5 (4)	3 (3)
Ear and labyrinth disorders	6 (5)	1 (1)	5 (4)	1 (1)
Vertigo	5 (4)	0	5 (4)	0
Vascular disorders	4 (3)	5 (4)	3 (2)	2 (2)
Investigations	3 (2)	3 (3)	2 (2)	2 (2)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	3 (2)	1 (1)	0	0
Renal and urinary disorders	3 (2)	2 (2)	0	1 (1)
Cardiac disorders	2 (2)	2 (2)	1 (1)	0
Reproductive system and breast disorders	2 (2)	1 (1)	0	0
Immune system disorders	1 (1)	0	0	0
Blood and lymphatic system disorders	0	2 (2)	0	0

AE, adverse effect; CBD, cannabidiol; THC, Δ^9-tetrahydrocannabinol.

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ports the consistent improvements in sleep seen in other clinical studies of this drug (Rog et al., 2005, 2007; Attal et al., 2006; Nurmikko et al., 2007). This provides further evidence for the efficacy of THC/CBD spray. Additionally, these improved sleep quality findings are also consistent with recent studies with smoked cannabis (Ware et al., 2010) and synthetic THC (Toth et al., 2012).

Analysis of the SGIC parameter evolution in the current study demonstrated a statistically significant treatment difference in favour of THC/CBD spray, with the most pronounced difference observed in the 'No Change' category, selected by a relatively high proportion of patients in the placebo group. The SGIC tool is considered the 'gold standard' measure of patient outcome in chronic pain trials (Dworkin et al., 2005). Based on this, our findings suggest that overall, patients can achieve important changes in quality of life with THC/CBD spray treatment.

Interestingly, other cannabinoid trials in which evoked pain was assessed reported some similar benefits to the current study (Svendsen et al., 2004; Abrams et al., 2007; Ware et al., 2010; Toth et al., 2012). Two RCTs that evaluated the effects of smoked cannabis on post-traumatic, post-surgical neuropathic pain (Ware et al., 2010) or HIV-associated sensory pain (Abrams et al., 2007) both demonstrated benefits in levels of pain intensity with active treatment. A further two trials that investigated different synthetic forms of THC, dronabinol (Svendsen et al., 2004) and nabilone (Toth et al., 2012) in the treatment of evoked pain, again demonstrated benefits in levels of pain intensity, as well as improvements in the quality of life and overall patient status, which is similar to the current study.

All other secondary endpoints that directly measured pain intensity showed improvements from baseline to the end of treatment, with treatment differences in favour of THC/CBD spray compared with placebo treatment, with only one exception. The punctate allodynia test score was found to improve with THC/CBD spray treatment, but the treatment difference was in favour of placebo. The analysis of rescue analgesia use also showed a tendency for reduced use in the THC/CBD spray treatment group compared with placebo, which could have impacted the pain questionnaire outcomes.

Throughout this study, existing analgesia was maintained based on ethical and clinical considerations. A variety of treatments for neuropathic pain have demonstrated efficacy and are in widespread use based on existing guidelines (Attal et al., 2006). To deprive a patient of these treatments during a placebo-controlled trial would not be ethical. Moreover, the use of combination treatments in clinical practice is becoming more commonplace due to the understanding that multiple pain mechanisms contribute to neuropathic pain (Woolf, 2004; Wade et al., 2010). Adding THC/CBD spray to a mixture of pain treatments, which work by different mechanisms, should not impede the activity of THC/CBD spray. However, if the other treatments are providing partial pain relief, this could reduce the magnitude of benefit derived from THC/CBD spray. The patients recruited for this trial were often very resistant to pharmacological therapy, so to show a 30% improvement in pain intensity in a proportion of patients was a clinically significant achievement.

The self-titration regimen used was chosen for a number of reasons, including the variable threshold of individual patients to the pharmacodynamic effects of THC/CBD spray (Rog et al., 2005; Attal et al., 2006). Having a self-titration schedule allowed patients to optimize their dose based on their own efficacy and tolerability.

In terms of safety, THC/CBD spray was well tolerated in this study, with low levels of intoxication experienced, and no evidence of tolerance developing, since there was a stable dose pattern following initial titration. The most common treatment-emergent, treatment-related events were dizziness, nausea, fatigue and dysgeusia (distortion of sense of taste). These AEs have been observed in other clinical studies with THC/CBD spray and are recognized as having a possible causal relationship to the study medication (Rog et al., 2005; Nurmikko et al., 2007; Wade et al., 2010). The increased incidence of AEs in certain SOCs with THC/CBD spray treatment compared with placebo (i.e., 'psychiatric disorders', 'nervous system disorders', 'gastrointestinal disorders' and 'general disorders and administration site conditions') have also been previously reported in other clinical trials with THC/CBD spray (Rog et al., 2005; Nurmikko et al., 2007; Wade et al., 2010). Psychiatric events such as dissociation and disorientation are known to be common in clinical trials with THC/CBD spray and are representative of a cannabis 'high' (Wade, 2012). A review of 805 THC/CBD spray patients versus 741 placebo patients found that 4% taking THC/CBD spray versus 0.5% taking placebo experienced disorientation, while 1.7% taking THC/CBD spray versus 0.1% taking placebo experienced dissociation (Wade, 2012). While the incidence of these two specific AEs was higher in this study, this may have been due to the titration regimen adopted. Indeed, a slower up-titration administration regimen for THC/CBD spray (over a 10-day period) was associated with a

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lower number of AEs in later studies (Collin et al., 2010; Novotna et al., 2011). In clinical trials of THC/CBD spray using a slow up-titration schedule, the incidence of psychiatric AEs is reduced from 15% to 8% compared with the original more aggressive regimen adopted in this study (Wade, 2012).

A total of 10 SAEs were experienced by patients receiving THC/CBD spray; however, none was considered to be treatment-related. There were no consistent patterns of difference between THC/CBD spray and placebo for haematology, biochemistry and urinalysis parameters. Furthermore, changes in vital signs for pulse rate and systolic blood pressure were unremarkable compared with baseline.

4.1 Study limitations

The presence of a substantial proportion of non-responders in this study suggests that the analysis of mean changes may not be the most appropriate means of identifying whether the medication has a clinically useful effect, since the lack of improvement in the non-responders would dilute the improvement seen in responders. In clinical practice, non-responders to treatment would be unlikely to remain on a non-effective drug and would therefore not contribute to understanding the utility of the medicine in the population of patients for whom it is suitable. This dilemma has been discussed by McQuay et al. (2008).

Another potential study limitation was the inclusion of multiple aetiologies of PNP leading to considerable clinical trial heterogeneity. The issue of clinical trial heterogeneity in patients with neuropathic pain has been well-documented, and several other controlled trials of promising new therapeutic candidates have been negative (Baron et al., 2012). By contrast, a variety of neuropathic pain studies in heterogeneous populations such as the current study have reported positive results in terms of pain scores (Serpell, 2002; Rowbotham et al., 2003), including studies in which vaporized cannabis (Wilsey et al., 2013) and cannabis cigarettes (Wilsey et al., 2008) were used, although slightly different pain scales were adopted than those used in the current study. Several clinical trials and post-hoc analyses have shown greater efficacy of the study drug when patients are sub-grouped based on baseline sensory symptoms and/or pain thresholds (Edwards et al., 2006; Simpson et al., 2010; Campbell et al., 2012). As such, future studies that incorporate sensory profiling may reveal specific subgroups of patients in which THC/CBD spray is efficacious.

A potential drawback of the maximum dose of 24 daily sprays adopted in this study was the potential for a 'placebo effect', which may have diminished the positive results seen with THC/CBD spray. While the treatment difference in favour of THC/CBD spray increased with increasing daily doses of study medication, this effect appeared to drop off at a dose of around 14–15 sprays per day. At a similar dose, however, the proportion of responders in the placebo treatment group was still increasing markedly with increasing numbers of daily sprays. This suggests that patients who took higher mean daily doses of placebo perceived a benefit in the subjective pain severity score. The consequence of this effect is an apparent decrease in the true treatment advantage of THC/CBD spray over placebo, observed at lower daily doses. These findings suggest that future studies would benefit from a reduction in the current dose ceiling of 24 sprays per day, thus allowing comparison of the two treatment groups at similar mean doses.

5. Conclusions

In conclusion, this study has shown that in a meaningful proportion of otherwise treatment-resistant patients, clinically important improvements in their pain, sleep quality and global impression of change in the severity of their condition were obtained by taking THC/CBD spray. There is also a possibility that these results may have been more strongly in favour of THC/CBD spray if the upper dose level had been capped to below 24 sprays daily, and a slower titration regimen had been adopted in an attempt to improve the overall tolerability and its effect of early withdrawals and, secondarily, to reduce the placebo response. Reassuringly, there was no evidence of tolerance developing and few patients reported experiencing severe AEs. Taken together, these finding are encouraging and suggest that treatment of PNP associated with allodynia with THC/CBD spray could bring significant benefit to patients.

Author contributions

All authors made a substantial contribution to the acquisition and interpretation of the data, critically reviewed the article and approved the final version for publication.

References

Abrams, D.I., Jay, C.A., Shade, S.B., Vizoso, R.N., Reda, H., Press, S., Kelly, M.E., Rowbotham, M.C., Petersen, K.L. (2007). Cannabis in painful HIV-associated sensory neuropathy. A randomised placebo-controlled trial. *Neurology* 68, 515–521.

Attal, N., Cruccua, G., Haanpää, M., Hansson, P., Jensen, T.S., Nurmikko, T., Sampaio, C., Sindrup, S., Wiffen, P., EFNS Task Force. (2006). EFNS guidelines on pharmacological treatment of neuropathic pain. *Eur J Neurol* 13(11), 1153–1169.

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Backonja, M., Serra, J. (2004). Pharmacologic management part 1: Better studied neuropathic pain diseases. *Pain Med* 5, S28–S47.

Baron, R., Förster, M., Binder, A. (2012). Subgrouping of patients with neuropathic pain according to pain-related sensory abnormalities: A first step to a stratified treatment approach. *Lancet Neurol* 11(11), 999–1005.

Berman, J.S., Symonds, C., Birch, R. (2004). Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: Results of a randomized controlled trial. *Pain* 112, 299–306.

Bouhassira, D., Lanteri-Minet, M., Attal, N., Laurent, B., Touboul, C. (2008). Prevalence of chronic pain with neuropathic characteristics in the general population. *Pain* 136, 380–387.

Boureau, F., Legallicier, P., Kabir-Ahmadi, M. (2003). Tramadol in post-herpetic neuralgia: A randomised, double-blind, placebo-controlled trial. *Pain* 104, 323–331.

Campbell, C.M., Kipnes, M.S., Stouch, B.C., Brady, K.L., Kelly, M., Schmidt, W.K., Petersen, K.L., Rowbotham, M.C., Campbell, J.N. (2012). Randomized control trial of topical clonidine for treatment of painful diabetic neuropathy. *Pain* 153(9), 1815–1823.

Casarett, D., Karlawish, J., Sankar, P., Hirschman, K., Asch, D.A. (2001). Designing pain research from the patients' perspective: What trial end-points are important to patients with chronic pain? *Pain Med* 2, 309–316.

Cleeland, C.S., Ryan, K.M. (1994). Pain assessment: Global use of the Brief Pain Inventory. *Ann Acad Med Singapore* 23(2), 129–138.

Collin, C., Ehler, E., Waberzinek, G., Alsindi, Z., Davies, P., Powell, K., Notcutt, W., O'Leary, C., Ratcliffe, S., Nováková, I., Zapletalova, O., Piková, J., Ambler, Z. (2010). A double-blind, randomized, placebo-controlled, parallel-group study of Sativex, in subjects with symptoms of spasticity due to multiple sclerosis. *Neurol Res* 32(5), 451–459.

Dworkin, R.H., Turk, D.C., Farrar, J.T., Haythornewaite, J.A., Jensen, M.P., Katz, N.P., Kerns, R.D., Stucki, G., Allen, R.R., Bellamy, N., Carr, D.B., Chandler, J., Cowan, P., Dionne, R., Galer, B.S., Hertz, S., Jadad, A.R., Kramer, L.D., Manning, D.C., Martin, S., McCormick, C.G., McDermott, M.P., McGrath, P., Quessy, S., Rappaport, B.A., Robbins, W., Robinson, J.P., Rothman, M., Royal, M.A., Simon, L., Stauffer, J.W., Stein, W., Tollett, J., Wernicke, J., Witter, J. (2005). Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain* 113, 9–19.

Edwards, R.R., Haythornthwaite, J.A., Tella, P., Max, M.B., Raja, S. (2006). Basal heat pain thresholds predict opioid analgesia in patients with postherpetic neuralgia. *Anesthesiology* 104(6), 1243–1248.

Howlett, A.C., Barth, F., Bonner, T.I., Cabral, G., Casellas, P., Devane, W.A., Felder, C.C., Herkenham, M., Mackie, K., Martin, B.R., Mechoulam, R., Pertwee, R.G. (2002). International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. *Pharmacol Rev* 54(2), 161–202.

Jensen, T.S., Gottrup, H., Sindrup, S.H., Bach, F.W. (2001). The clinical picture of neuropathic pain. *Eur J Pharmacol* 429, 1–11.

Karst, M., Salim, K., Burstein, S., Conrad, I., Hoy, L., Schneider, U. (2003). Analgesic effect of the synthetic cannabinoid CT3 on chronic neuropathic pain. A randomized controlled trial. *JAMA* 290(13), 1757–1762.

McQuay, H.J., Derry, S., Moore, R.A., Poulain, P., Legout, V. (2008). Enriched enrolment with randomised withdrawal (EERW): Time for a new look at clinical trial design in chronic pain. *Pain* 135, 217–220.

MHRA Public Assessment Report. (2010). Nabiximols Oromucosal Spray (delta-9-tetrahydrocannabinol and cannabidiol) – PL 18024/0009. UK/H/2462/001/DC. http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con084961.pdf (accessed January 2012).

Novotna, A., Mares, J., Ratcliffe, S., Novakova, I., Vachova, M., Zapletalova, O., Gasperini, C., Pozzilli, C., Cefaro, L., Comi, G., Rossi, P., Ambler, Z., Stelmasiak, Z., Erdmann, A., Montalban, X., Klimek, A., Davies, P., Sativex Spasticity Study Group. (2011). A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols (Sativex®), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis. *Eur J Neurol* 18, 1122–1131.

Nurmikko, T.J., Serpell, M.G., Hoggart, B., Toomey, P.J., Morlion, B.J., Haines, D. (2007). Sativex successfully treats neuropathic pain characterised by allodynia: A randomised, double-blind, placebo-controlled clinical trial. *Pain* 133, 210–220.

Rasmussen, P.V., Sindrup, S.H., Jensen, T.S., Bach, F.W. (2004). Therapeutic outcome in neuropathic pain: Relationship to evidence of nervous system lesion. *Eur J Neurol* 11, 545–553.

Rice, A.S., Maton, S.; Postherpetic Neuralgia Study Group. (2001). Gabapentin in post herpetic neuralgia: A randomised, double blind, placebo controlled study. *Pain* 94(2), 215–224.

Rog, D.J., Nurmikko, T.J., Friede, T., Young, C.A. (2005). Randomized controlled trial of cannabis based medicine in central pain due to multiple sclerosis. *Neurology* 65, 812–819.

Rog, D.J., Nurmikko, T.J., Young, C.A. (2007). Oromucosal delta-9-tetrahydrocannabinol/cannabidiol for neuropathic pain associated with multiple sclerosis: An uncontrolled, open-label, 2-year extension trial. *Clin Ther* 29(9), 2068–2079.

Rowbotham, M., Harden, N., Stacey, B., Bernstein, P., Magnus-Miller, L. (1998). Gabapentin for the treatment of post herpetic neuralgia. *JAMA* 280, 1837–1842.

Rowbotham, M.C., Twilling, L., Davies, P.S., Reisner, L., Taylor, K., Mohr, D. (2003). Oral opioid therapy for chronic peripheral and central neuropathic pain. *N Engl J Med* 348(13), 1223–1232.

Russo, E.B. (2011). Taming THC: Potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *Br J Pharmacol* 163(7), 1344–1364.

Serpell, M.G., Neuropathic Pain Study Group. (2002). Gabapentin in neuropathic pain syndromes: A randomised, double-blind, placebo-controlled trial. *Pain* 99, 557–566.

Simpson, D.M., Schifitto, G., Clifford, D.B., Murphy, T.K., Durso-De Cruz, E., Glue, P., Whalen, E., Emir, B., Scott, G.N., Freeman, R., 1066 HIV Neuropathy Study Group. (2010). Pregabalin for painful HIV neuropathy: A randomized, double-blind, placebo-controlled trial. *Neurology* 74(5), 413–420.

Stacey, B.R., Dacosta DiBonaventura, M., Martin, S., Bell, C.F. (2010). Chronological Characteristics of Painful Diabetic Peripheral Neuropathy. American Pain Society ASM, Abstract 23.

Svendsen, K.B., Jensen, T.S., Bach, F.W. (2004). Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. *BMJ* 329, 253–260.

The Committee For Medicinal Products For Human Use (CHMP). Guideline on Clinical Investigation of Medicinal Products Intended for the Treatment Of Neuropathic Pain London, 18 November 2004 CHMP/EWP/252/03.

The Euroqol Group. (1990). Euroqol – a new facility for the measurement of health-related quality of life. *Health Policy* 16, 199–208.

Torrance, N., Smith, B.H., Bennett, M.I., Lee, A.J. (2006). The epidemiology of chronic pain of predominantly neuropathic origin. Results from a general population survey. *Pain* 7, 281–289.

Toth, C., Mawani, S., Brady, S., Chan, C., Liu, C., Mehina, E., Garven, A., Bestard, J., Korngut, L. (2012). An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind, placebo-controlled, parallel assignment efficacy study of nabilone as adjuvant in the treatment of diabetic peripheral neuropathic pain. *Pain* 153(10), 2073–2082.

Turk, D.C., Dworkin, R.H. (2004). What should be the core outcomes in chronic pain clinical trials? *Arthritis Res Ther* 6, 151–154.

Wade, D. (2012). Evaluation of the safety and tolerability profile of Sativex: Is it reassuring enough? *Expert Rev Neurother* 12(4 Suppl), 9–14.

Wade, D.T., Collin, C., Stott, C., Duncombe, P. (2010). Meta-analysis of the efficacy and safety of Sativex (nabiximols) on spasticity in people with multiple sclerosis. *Mult Scler* 16, 707–714.

Ware, M.A., Wang, T., Shapiro, S., Robinson, A., Ducruet, T., Huynh, T., Gamsa, A., Bennett, G.J., Collet, J.P. (2010). Smoked cannabis for chronic neuropathic pain: A randomized controlled trial. *CMAJ* 182(14), E694–E701.

Wilsey, B., Marcotte, T., Deutsch, R., Gouaux, B., Sakai, S., Donaghe, H. (2013). Low-dose vaporized cannabis significantly improves neuropathic pain. *J Pain* 14(2), 136–148.

Wilsey, B., Marcotte, T., Tsodikov, A., Millman, J., Bentley, H., Gouaux, B., Fishman, S. (2008). A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. *J Pain* 9(6), 506–521.

Woolf, C.J. (2004). Dissecting out mechanisms responsible for peripheral neuropathic pain: Implications for diagnosis and therapy. *Life Sci* 74, 2605–2610.

Woolf, C.J., Max, B.M. (2001). Mechanism-based pain diagnosis. *Anaesthesiology* 95, 241–249.

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