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ORIGINAL COMMUNICATION

A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis

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Abstract Central neuropathic pain (CNP) occurs in many multiple sclerosis (MS) patients. The provision of adequate pain relief to these patients can very difficult. Here we report the first phase III placebo-controlled study of the efficacy of the endocannabinoid system modulator delta-9-tetrahydrocannabinol (THC)/cannabidiol (CBD) oromucosal spray (USAN name, nabiximols; Sativex, GW Pharmaceuticals, Salisbury,Wiltshire, UK), to alleviate CNP. Patients who had failed to gain adequate analgesia from existing medication were treated with THC/CBD spray or placebo as an add-on treatment, in a double-blind manner, for 14 weeks to investigate the efficacy of the medication in MS-induced neuropathic pain. This parallel-group phase of the study was then followed by an 18-week randomized-withdrawal study (14-week open-label treatment period plus a double-blind 4-week randomized-withdrawal phase) to investigate time to treatment failure and show maintenance of efficacy. A total of 339 patients were randomized to phase A (167 received THC/CBD spray and 172 received placebo). Of those who completed phase A, 58 entered the randomized-withdrawal phase. The primary endpoint of responder analysis at the 30 % level at week 14 of phase A of the study was not met, with 50 % of patients on THC/CBD spray classed as responders at the 30 % level compared to 45 % of patients on placebo ($p = 0.234$). However, an interim analysis at week 10 showed a statistically significant treatment difference in favor of THC/CBD spray at this time point ($p = 0.046$). During the randomized-withdrawal phase, the primary endpoint of time to treatment failure was statistically significant in favor of THC/CBD spray, with 57 % of patients receiving placebo failing treatment versus 24 % of patients from the THC/CBD spray group ($p = 0.04$). The mean change from baseline in Pain Numerical Rating Scale (NRS) ($p = 0.028$) and sleep quality NRS ($p = 0.015$) scores, both secondary endpoints in phase B, were also statistically significant compared to placebo, with estimated treatment differences of −0.79 and 0.99 points, respectively, in favor of THC/CBD spray treatment. The results of the current investigation were equivocal, with conflicting findings in the two phases of the study. While there were a large proportion of responders to THC/CBD spray treatment during the phase A double-blind period, the primary endpoint was not met due to a similarly large number of placebo responders. In contrast, there was a marked effect in phase B of the study, with an increased

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

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time to treatment failure in the THC/CBD spray group compared to placebo. These findings suggest that further studies are required to explore the full potential of THC/CBD spray in these patients.

Keywords Cannabidiol · Cannabinoid · Central neuropathic pain · Delta-9-tetrahydrocannabinol · Multiple sclerosis · THC/CBD oromucosal spray

Introduction

Multiple sclerosis (MS) is a progressive inflammatory disease of the central nervous system (CNS) caused by axonal demyelination. Thought to be autoimmune in origin, MS results in dysfunction of the CNS, causing a range of symptoms including spasticity, spasms, fatigue, bladder dysfunction and pain. With an estimated prevalence of 50–120 per 100,000, it is the most common cause of neurological disability among young adults in the United Kingdom (UK) [1, 2].

Central neuropathic pain (CNP) caused by a lesion or dysfunction of the CNS is a common symptom of MS, affecting between 17 and 52 % of MS patients [3–9]. This type of pain can be difficult to treat, with current treatment regimens including tricyclic antidepressants, gabapentinoids, and carbamazepine [10–12], causing side effects that may be problematic. A class of compounds called cannabinoids have been shown to have therapeutic effects in animal models of CNP via interactions with specific cannabinoid receptors (CBRs) [13]. Endogenously released cannabinoids, such as anandamide and 2-arachidonoyl glycerol, act via these CBRs, designated CB_1 and CB_2 [14]. CB_1 receptors are found predominantly at nerve terminals where they mediate inhibition of neurotransmitter release. CB_2 receptors are expressed mainly by immune cells, the functions of which include the modulation of cytokine release and of immune cell migration both within and outside the CNS [15]. CB_1 and CB_2 receptors are targeted by agonists produced in mammalian tissues, and this system of receptors and endocannabinoids together constitute the endocannabinoid system. Cannabinoids may also demonstrate activity at other receptors including the orphan G protein-coupled receptor 55, transient receptor potential vannilloid-1 and adenosine receptors [16–18].

Delta-9-tetrahydrocannabinol (THC)/cannabidiol (CBD) spray is derived from extracts of the plant *Cannabis sativa* L., and is an endocannabinoid system modulator. It contains THC and CBD in an approximate 1:1 ratio, and was recently approved for use in several European countries for treating spasticity in MS patients [19].

A recent study in central MS pain using THC/CBD spray showed a beneficial effect over placebo [20]. During phase II and III studies, THC/CBD spray was found to have analgesic properties that were effective in relieving neuropathic pain. These studies also suggested that the medication was well tolerated and could also improve sleep and quality of life. A 2-year, open-label follow-up study showed continued effectiveness with THC/CBD spray, and no evidence of tolerance was seen in the 28 patients who completed the study [21]. Furthermore, a meta-analysis of THC/CBD spray, dronabinol (synthetic THC) and CBD in neuropathic and MS-related pain revealed statistically significant pain relief in these studies [22].

This study assessed the efficacy of THC/CBD spray on CNP due to MS, as well as evaluating the effect of the medication on sleep quality, quality of life, and patients perception of CNP after 14 weeks of treatment (phase A, double-blind). Phase B of the study (randomized-withdrawal) investigated the maintenance of efficacy after long-term treatment with THC/CBD spray in the indication of CNP in MS, and assessed the absence or occurrence of withdrawal symptoms.

Methods

The study was conducted in two phases and took place in 33 study sites (UK, 12; Czech Republic, seven; Canada, five; Spain, five and France, four). It was approved by the relevant independent review board/ethics committee in each of the countries, and was conducted in accordance with good clinical practice guidelines.

Phase A was a double-blind, randomized, placebo-controlled, 14-week treatment phase to evaluate the efficacy of THC/CBD spray in the treatment of CNP in MS patients in addition to existing treatment regimens. A 1-week baseline period allowing for dosing optimization preceded the 14-week treatment phase. Response was assessed using a validated self-reported 0–10 point numerical rating scale (NRS), where mean daily CNP due to MS was scored. Phase B was a 14-week open-plan treatment phase consisting of a 2-week re-titration period and 12-week stable dose phase with THC/CBD spray, with an additional 4-week randomized-withdrawal phase, where patients received either THC/CBD spray or placebo in a double-blind manner. The maintenance of efficacy with long-term treatment with THC/CBD spray was investigated, and the frequency and severity of withdrawal symptoms assessed.

Randomization

Randomization occurred using a pre-determined computer-generated randomization code in which treatment allocation was stratified by center, and used randomly permuted blocks of variable sizes. Separate randomization schemes, using the same strategy, were produced for each part of the

study. Patients, investigators, and those assessing the data were therefore blinded to the patients' treatment allocation.

Main inclusion and exclusion criteria

Main study entry inclusion criteria

Eligible subjects were to have CNP due to MS, of at least 3 months duration. Subjects were also to have a sum score of at least 24 on a pain 0–10 point NRS on the last 6 days during the baseline period. In addition, their analgesic regimen was to be stable for at least 2 weeks preceding the study entry day.

Phase B (randomized-withdrawal)

French and Czech patients who had completed phase A of the study were invited to take part in phase B. Patients were required to have received an average of three or more sprays of THC/CBD per day in the 7 days prior to completion of phase A, shown tolerability to the study medication, and maintained a stable treatment regimen throughout the study for all neuropathic pain medications.

Main exclusion criteria

Patients with severe pain from other concomitant conditions were excluded. This included pain of a nociceptive, musculoskeletal (including spasms), peripheral neuropathic or psychogenic origin, or due to trigeminal neuralgia. Patients were also excluded if they had other pain that was not of a central neuropathic origin thought by the investigator to be of a nature or severity to interfere with the patient's assessment of neuropathic pain due to MS. Patients with a history of significant psychiatric (other than depression associated with their underlying condition), renal, hepatic, cardiovascular, or convulsive disorders, or with a sensitivity to cannabis or cannabinoids, were also excluded. Participants who had experienced an adverse event (AE) in phase A were also excluded from phase B.

Treatment groups and doses

A pump-action oromucosal spray delivered the study medication. Each 100-µl actuation of active medication delivered 2.7 mg of THC and 2.5 mg of CBD to the oral mucosa. Placebo delivered the excipient plus colorants. Patients were restricted to a maximum of 12 sprays per 24-h period. During the baseline period, patients self-titrated, titrating upwards via a pre-defined escalation scheme to reach their optimal dose depending on efficacy, tolerability, and maximum permitted dose. To escalate the dose to a maximum of 12 daily sprays during the phase B re-titration period, patients were instructed to administer one spray on days 1 and 2, two sprays on days 3 and 4, three sprays on day 5, four on day 6, five on day 7 and so on until reaching the maximum dose of 12 daily sprays on day 14. Re-titration took place as it was assumed that a number of patients who received placebo in phase A would embark on active treatment in phase B. Since phase A of the study was still blinded, all patients underwent re-titration in phase B.

Study endpoints

Efficacy endpoints

The primary efficacy endpoint for phase A was the response to treatment, defined as an improvement of 30 % or more in patient's mean pain NRS score from baseline to the last week of treatment in phase A. In phase B, it was time to treatment failure during the randomized-withdrawal period.

Secondary efficacy endpoints for both phases included the Brief Pain Inventory—Short Form, Subject Global Impression of Change, and sleep quality assessments.

Safety endpoints

In both phases, the incidences of AEs were assessed.

Statistical methods

Sample size

A previous 4-week GW study in patients with CNP due to MS resulted in 37.5 and 51.5 % of placebo and THC/CBD spray patients, respectively, achieving a 30 % reduction (improvement) in mean pain NRS scores; representing an odds ratio of 1.71 for responding with THC/CBD spray compared with placebo. Given the longer duration of this study, it was assumed that the odds ratio achieved would be 1.90, leading to an anticipated responder rate of 53.3 % with THC/CBD spray, assuming the placebo responder rate did not change. Therefore, to obtain a 30 % response with THC/CBD spray compared with placebo, a total of 312 patients (156 in each group) were required in order to detect, with 80 % power at the $\alpha = 0.05$ level, a statistically significant difference between the treatment groups. It was estimated that between 60 and 80 patients would be eligible to enroll in phase B of the study. However, there was no formal intended sample size for phase B.

Phase A

The baseline CNP NRS value was the average of the 7 days scores in baseline week one, with the variable for

analysis being the change in pain NRS scores from baseline to end of treatment (average of final 7 days scores). The primary analysis was performed on the intention-to-treat (ITT) population and a two-sided significance test was used in all comparisons at the 5 % level of significance and a 95 % confidence interval (CI) was presented for the difference between baseline and endpoint.

Phase B

Time to treatment failure was analyzed using Kaplan–Meier survival analysis methodology and proportional odds modeling, with randomized treatment as a factor. Secondary efficacy variables for both studies were analyzed using analysis of covariance (ANCOVA).

Results

A summary of breakdown of patients enrolled in phases A and B of the study are shown in Fig. 1a, b, respectively, and respective study population demographics are displayed in Table 1A, B. The demographics between the two study groups were similar with a mean duration of MS in excess of 11 years, and neuropathic pain in excess of 5 years. During phase A, patients receiving placebo administered an average of 11.1 (SD = 4.6) daily sprays compared to 8.8 (SD = 3.87) sprays in the THC/CBD group. In the open-label stage of phase B, patients took an average of 6.7 (SD = 2.48) daily sprays. During randomized-withdrawal the active treatment group administered on average 7.3 (SD = 2.42) sprays daily compared with 8 (SD = 2.72) daily sprays by the placebo group (Table 1A, B).

Concomitant medication

Paracetamol was provided for rescue analgesic use during both study phases. The majority of patients in both phases were receiving this and other concomitant analgesic medications (details presented in Table 2). As would be expected in this group of patients, most were taking medication other than analgesics during the course of the study (92 % phase A; 93 % phase B).

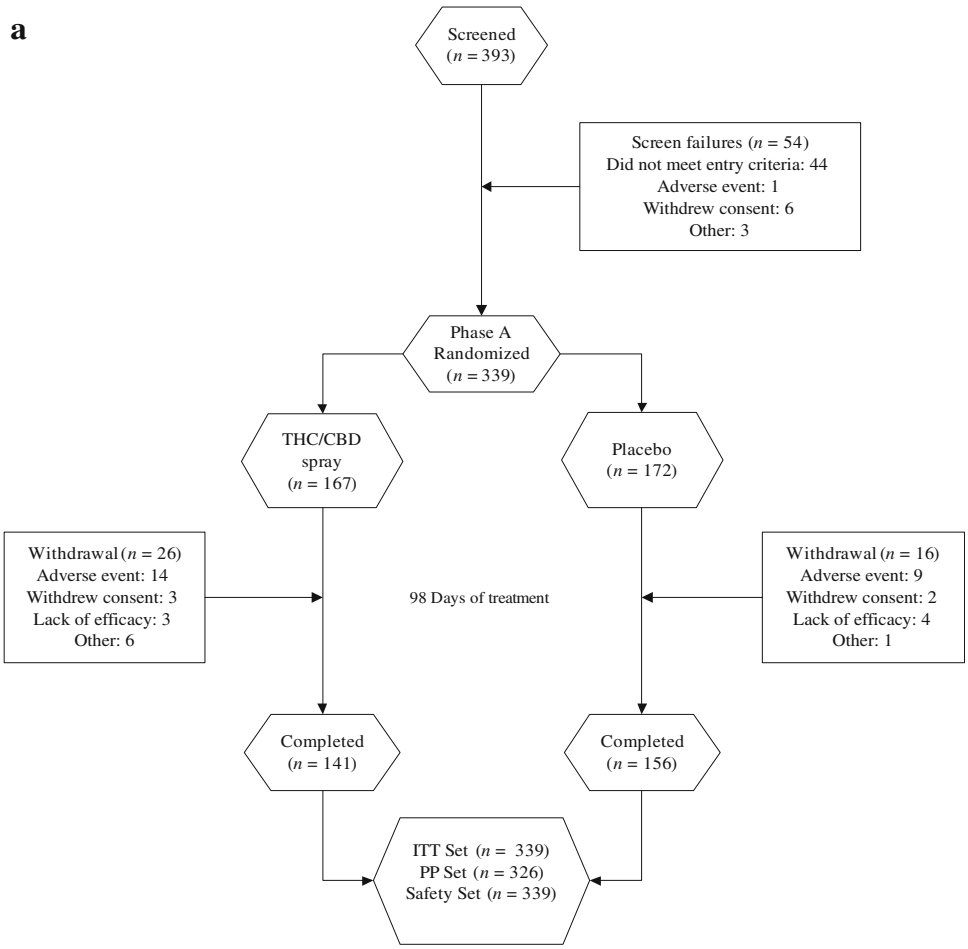
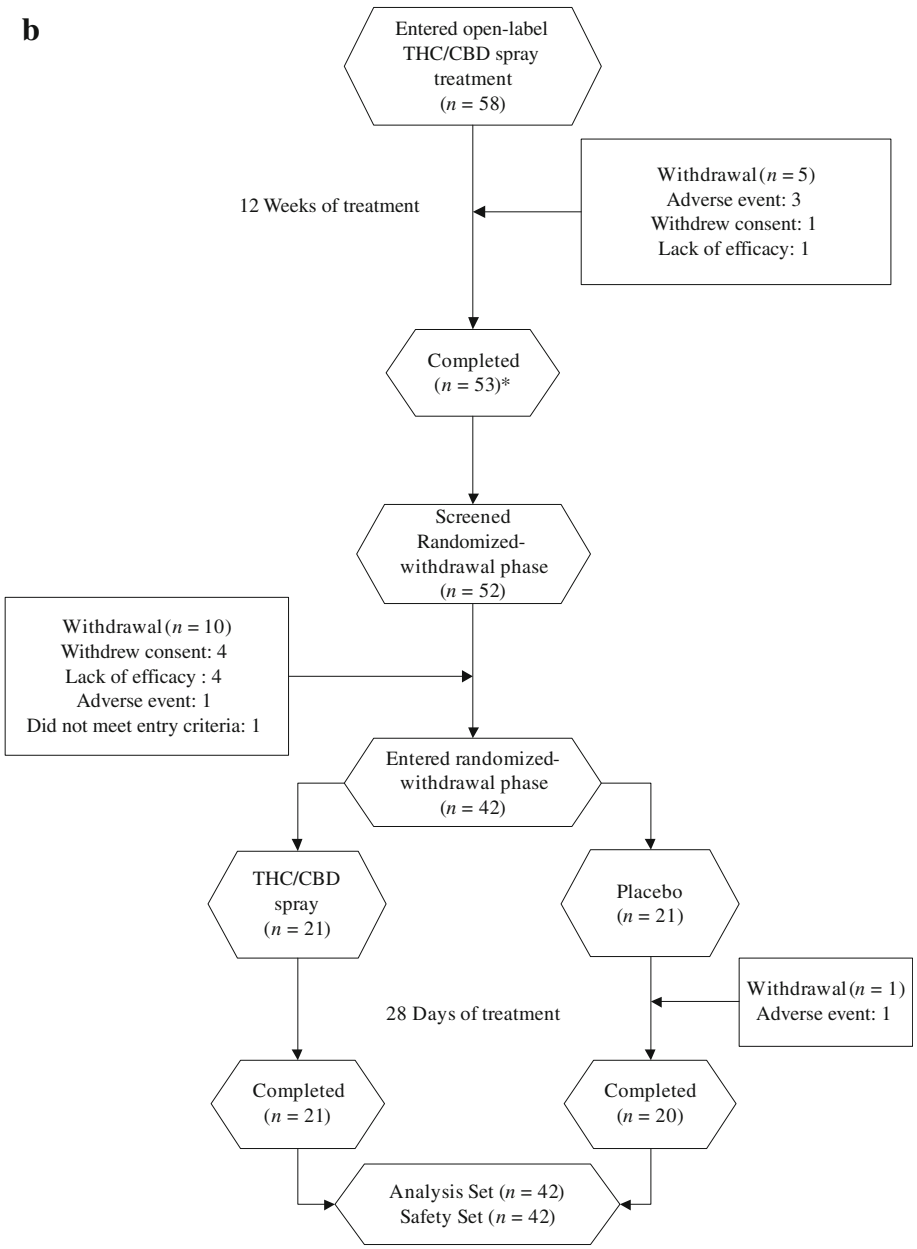


Fig. 1 Disposition of patients in phase A (**A**) and phase B (**B**). *One Subject completed the open-label part of Phase B but at the start of the randomized-withdrawal phase no longer wanted to continue in the study as they had experienced AEs

Fig. 1 continued



Primary analysis: responder analysis

Phase A

The number of responders at the 30 % improvement level in mean pain NRS score in the last week of treatment totaled 50 % in the THC/CBD spray group compared to 45 % in the placebo group (odds ratio 1.31 [95 % CI: 0.84–2.04 points]: $p = 0.234$) (Fig. 2). At week 10 of the study, there was a significant treatment difference in favor of THC/CBD spray (odds ratio 1.61 [95 % CI: 1.01–2.57]: $p = 0.046$) (Fig. 2). At the end of treatment, the mean reduction in pain 0–10 NRS score for THC/CBD spray treatment was −1.93 points (from a baseline score of 6.55 ± 1.35–4.54 ± 2.24) compared to −1.76 points (from a baseline score of 6.61 ± 1.29–4.73 ± 2.26) for the placebo group, an estimated treatment difference of 0.17 points in favor of THC/CBD spray, which did not reach statistical significance (95 % CI: −0.62 to 0.29 points; $p = 0.47$) (Fig. 3).

Phase B

A marked increase in the time to treatment failure was observed in the active treatment group in phase B, with only 24 % of patients failing treatment with THC/CBD spray compared to 57 % from the placebo group, which reached statistical significance (logrank test for equality of curves $p = 0.04$) (Fig. 4). The hazard ratio (0.374) for time

Table 1 Demographics and baseline characteristics for all patients who completed phase A of the study (**A**) and phase B of the study (**B**)

	No. of patients (%)		
	THC/CBD spray ($n = 167$)	Placebo ($n = 172$)	Total ($n = 339$)
A			
Gender			
Male	54 (32)	55 (32)	109 (32)
Female	113 (68)	117 (68)	230 (68)
Ethnic origin			
White/Caucasian	165 (99)	167 (97)	332(98)
Black/African American	2 (1)	2 (1)	4 (1)
Asian	0 (0)	2 (1)	2 (1)
Other	0 (0)	1 (1)	1 (<0.5)
Previous cannabis use in the last year	11 (7)	10 (6)	21 (6)
	Mean (SD)		
Age (years)	48.42 (10.43)	49.51 (10.50)	48.97 (10.47)
BMI (kg/m^2)	26.64 (5.27)	26.02 (4.97)	26.33 (5.12)
Duration of MS (years)	11.42 (8.00)	12.53 (8.50)	11.99 (8.26)
Duration of CNP (years)	5.59 (6.12)	5.33 (4.80)	5.46 (5.49)
Baseline pain NRS	6.55 (1.35)	6.61 (1.29)	6.58 (1.32)
Subtype of MS			
Primary progressive	18 (11)	22 (13)	40 (12)
Secondary progressive	65 (39)	71 (41)	136 (40)
Relapsing/remitting	80 (48)	77 (45)	157 (46)
Progressive relapsing	4 (2)	2 (1)	6 (2)
Disease-modifying treatments taken during phase A			
Total number of patients	100 (60)	100 (58)	200 (59)
Glucocorticoids	59 (35)	73 (42)	132 (39)
Interferons	44 (26)	39 (23)	83 (24)
Other immunosuppressive agents	29 (17)	28 (16)	57 (17)
Selective immunosuppressive agents	17 (10)	15 (9)	32 (9)
Nitrogen mustard analogues	6 (4)	13 (8)	19 (6)
Folic acid analogues	7 (4)	5 (3)	12 (4)

	No. of subjects (%)			
	Open-label	Randomized-withdrawal		
	THC/CBD spray ($n = 58$)	THC/CBD spray ($n = 21$)	Placebo ($n = 21$)	Total ($n = 42$)
B				
Gender				
Male	21 (36)	10 (48)	7 (33)	17 (40)
Female	37 (64)	11 (52)	14 (67)	25 (60)
Ethnic origin				
White/Caucasian	57 (98)	21 (100)	21 (100)	42 (100)
Previous cannabis use in the last year	2 (3)	0	1 (5)	1 (2)
	Mean (SD)			
Age (years)	48.00 (9.41)	46.20 (10.39)	49.82 (9.75)	48.01 (10.12)
BMI (kg/m^2)	25.32 (5.77)	24.88 (5.07)	26.66 (4.88)	25.77 (5.00)
Duration of MS (years)	11.96 (8.19)	12.56 (8.03)	10.43 (8.60)	11.50 (8.29)
Duration of CNP (years)	6.18 (6.98)	5.76 (5.87)	5.72 (8.97)	5.74 (7.48)

Table 1 continued

	No. of subjects (%)			
	Open-label	Randomized-withdrawal		
	THC/CBD spray ($n = 58$)	THC/CBD spray ($n = 21$)	Placebo ($n = 21$)	Total ($n = 42$)
Baseline pain NRS	6.60 (1.35)	6.21 (1.37)	6.49 (1.31)	6.35 (1.33)
Subtype of MS				
Primary progressive	4 (7)	3 (14)	0	3 (7)
Secondary progressive	22 (38)	4 (19)	9 (43)	13 (31)
Relapsing/remitting	29 (50)	14 (67)	11 (52)	25 (60)
Progressive relapsing	3 (5)	0	1 (5)	1 (2)
Disease-modifying treatments taken during phase				
Total number of patients	48 (83)	17 (81)	18 (86)	35 (83)
Folic acid analogues	1 (2)	–	–	–
Glucocorticoids	34 (59)	15 (71)	10 (48)	25 (60)
Interferons	10 (17)	3 (14)	6 (29)	9 (21)
Nitrogen mustard analogues	6 (10)	1 (5)	2 (10)	3 (7)
Other immunosuppressive agents	11 (19)	3 (14)	5 (24)	8 (19)
Selective immunosuppressive agents	11 (19)	4 (19)	4 (19)	8 (19)

to treatment failure was also in favor of THC/CBD spray, with the 90 % CI excluding unity, suggesting a real difference between treatments (90 % CI: 0.155–0.902; $p = 0.054$) (Fig. 4).

Secondary endpoints

Phase A

None of the secondary efficacy endpoints demonstrated a statistically significantly treatment difference in favor of THC/CBD spray (Table 3A).

Phase B

During phase B, the change in mean pain NRS score at the end of the treatment gave an estimated treatment difference of −0.79 points in favor of THC/CBD spray, a statistically significant difference in pain (90 % CI: −1.37 to −0.21 points; $p = 0.028$) (Table 3B).

During randomized-withdrawal, a significant difference in the sleep quality NRS score in favor of THC/CBD spray was observed, the results of which are summarized in Table 3B. All other secondary endpoints from phase B showed a treatment difference in favor of THC/CBD spray,

Table 2 Summary of all concomitant analgesic medications being used by randomized patients in phases A and B of the study

Medication class/name	No. of patients (%)				
	Phase A		Phase B		
			Open-label	Randomized-withdrawal	
	THC/CBD spray ($n = 167$)	Placebo ($n = 172$)	THC/CBD spray ($n = 58$)	THC/CBD spray ($n = 21$)	Placebo ($n = 21$)
Anticonvulsant	76 (46)	96 (56)	26 (45)	7 (33)	13 (62)
NSAID	58 (35)	57 (33)	20 (34)	8 (38)	7 (33)
Other analgesics	91 (54)	104 (60)	45 (78)	17 (81)	14 (67)
Tricyclic anti-depressants	75 (45)	73 (42)	21 (36)	6 (29)	9 (43)
Other opioid	33 (20)	31 (18)	10 (17)	4 (19)	4 (19)
Strong opioids	7 (4)	7 (4)	2 (3)	0	1 (5)
Antiarrhythmic	0	1 (1)	0	0	0
At least one analgesic	153 (92)	167 (97)	58 (100)	21 (100)	21 (100)

but only two reached statistical significance (see Table 3B).

Safety and tolerability

All AEs experienced by patients in phase A and B are displayed in Table 4A, B, respectively. During phase A, a total of 27 patients (8 %), 15 (9 %) in the THC/CBD spray group and 12 (7 %) in the placebo group, stopped study medication due to AEs. Of these, eight patients (2 %) (five [3 %] in the THC/CBD spray group and three [1 %] in the placebo group), permanently stopped study medication due to severe AEs and 18 (5 %) (12 in the THC/CBD spray arm and six in the placebo arm) were considered to be treatment-related. The majority of AEs leading to permanent cessation of study medication were within the nervous system disorders and gastrointestinal disorders system organ classes (SOCs). There was no significant difference in the number of patients that ceased study medication between the two arms of the study but there were twice the number of treatment-related AEs amongst patients ceasing study medication from the THC/CBD spray group than from the placebo group (Table 4A). Thirty-five patients (10 %) in phase A experienced a severe treatment-emergent AE, 21 (13 %) in the THC/CBD spray group and 14 (8 %) in the placebo group. AEs with severe intensity were observed most often in the nervous system disorders, gastrointestinal system disorders, and psychiatric system disorders SOCs. Overall, the difference in the incidence of severe events between the two treatment arms was small and insignificant. In the nervous system disorders SOC, there were twice as many patients with severe events in the THC/CBD spray group than in the placebo. In the psychiatric SOC, there were equal proportions of patients with severe events in the active and placebo study medication arms. No patient experienced a severe event on more than two occasions.

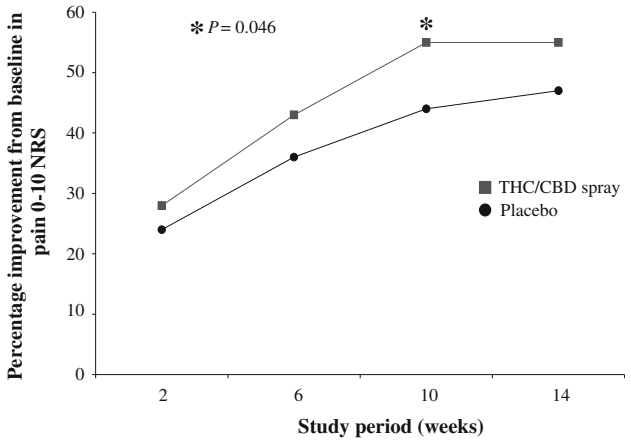


Fig. 2 Percentage of patients gaining a 30 % response improvement from baseline in pain 0–10 NRS (intention-to-treat analysis) in phase A of the study

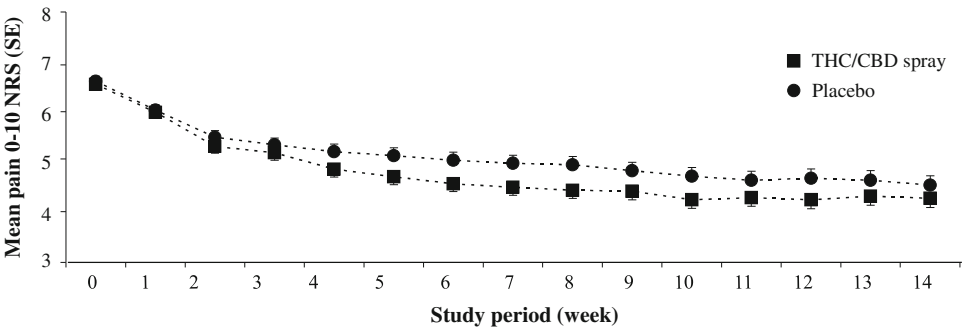


Fig. 3 Mean pain 0–10 NRS scores during the treatment period of phase A (intention-to-treat analysis)

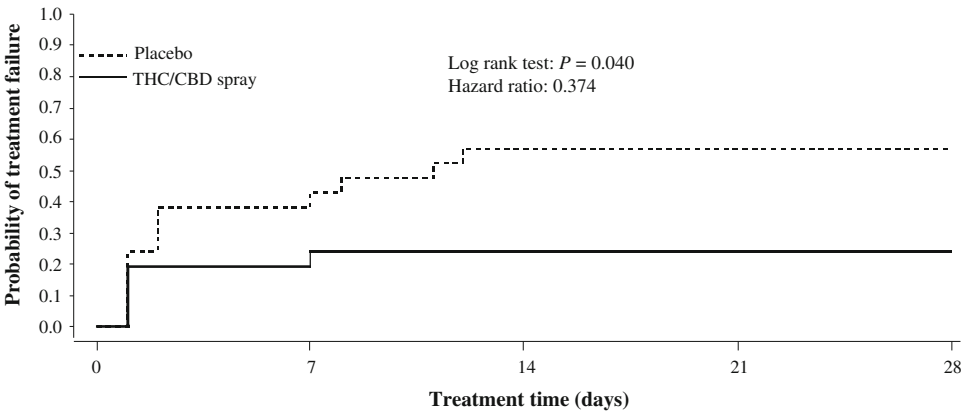


Fig. 4 Probability of treatment failure in patients receiving THC/CBD spray or placebo during randomized-withdrawal in phase B of the study

Table 3 Summary of primary and secondary efficacy results comparing mean values of THC/CBD spray vs. placebo, from baseline to end of treatment during phase A of the study (A) and phase B of the study (B)

Variable	Summary of primary and secondary efficacy endpoints: Phase A			
	THC/CBD spray (mean)	Placebo (mean)	Treatment difference	*p* value
A				
30 % responder	0.5	0.45	0.06	0.234
50 % responder	0.3	0.28	0.02	0.714
NPS	−12.41	−10.58	1.83	0.310
Sleep quality NRS	−1.96	−2.00	0.05	0.833
BPI-SF	−1.47	−1.35	−0.12	0.564
Breakthrough analgesia	−1.15	−0.91	−0.24	0.157
PDI	−3.25	−6.04	2.79	0.058
Spasticity NRS	−1.19	−1.09	−0.1	0.667
Bladder NRS	−0.56	−0.78	0.22	0.364
Spasm severity NRS	−1.06	−0.92	−0.14	0.548
Tremor NRS	−0.51	−0.77	0.25	0.216
Fatigue NRS	−0.96	−1.28	0.32	0.176
EQ-5D Health state index	0.05	0.07	−0.01	0.396
EQ-5D Health status VAS	7.20	5.26	1.94	0.383
SF-36				
Physical functioning	1.56	2.02	−0.45	0.785
Role physical	5.62	6.51	−0.89	0.694
Bodily pain	11.36	10.01	1.35	0.494
General health	2.32	4.02	−1.70	0.264
Vitality	3.72	6.47	−2.75	0.095
Social functioning	3.62	9.37	−5.75	0.020
Role emotion	−0.18	3.15	−3.33	0.216
Mental health	3.17	3.73	−0.56	0.733

	95 % confidence interval			
	Lower	Upper	Odds ratio	
SGIC	0.99	2.18	1.47	0.055

Procedure	Summary of primary and secondary efficacy endpoints: randomized-withdrawal (Phase B)			
	Primary efficacy measure: time to treatment failure			
	Test	Chi-square	*df*	*p* value
B				
Kaplan–Meier	Logrank	4.22	1	0.040
Proportional hazard regression (1)	Likelihood ratio	4.01	1	0.045
Proportional hazard regression (2)	Likelihood ratio	3.72	1	0.054

Variable	Secondary efficacy endpoints during randomized-withdrawal			
	THC/CBD spray (mean)	Placebo (mean)	Treatment difference	*p* value
IVRS pain NRS	−0.03	0.76	−0.79	0.028
NPS	−0.93	5.87	−6.8	0.153
Sleep quality NRS	−0.07	0.92	−0.99	0.015
Spasticity NRS	−0.12	0.63	−0.75	0.150
Bladder symptoms NRS	−0.10	0.60	−0.70	0.114

Table 3 continued

Variable	Secondary efficacy endpoints during randomized-withdrawal			
	THC/CBD spray (mean)	Placebo (mean)	Treatment difference	*p* value
Spasm severity NRS	−0.07	0.97	−1.05	0.095
Tremor NRS	0.00	0.20	−0.19	0.766
Fatigue NRS	−0.35	0.21	−0.56	0.439
	95 % confidence interval			
	Lower	Upper	Odds ratio	
SGIC	0.486	3.245	1.25	0.69

During the post-randomization part of phase B, the AE profile was similar between groups (Table 4B). The most common AEs in the THC/CBD spray group were dizziness, fatigue, somnolence, vertigo, and nausea. There were reports of three serious adverse events (SAE) during the course of this study. One patient (5 %) receiving THC/CBD spray experienced serious disorientation, and two patients, one (5 %) receiving THC/CBD spray and the other (5 %) receiving placebo experienced the SAE of suicidal ideation. Six patients (10 %) stopped their study medication permanently because of AEs in the open-label part of phase B. During this phase, four patients (11 %) had treatment-related events and all had previously been receiving placebo prior to entering phase B of the study. In the randomized-withdrawal phase of the study, only one patient on placebo ceased to participate in the study permanently as a result of a severe SAE of accidental injury. The SAE was considered unrelated to the placebo medication.

Discussion

The results of phase A of this study failed to show a significant difference between THC/CBD spray and placebo in the primary and in the majority of secondary efficacy endpoints. However, the results from a phase A intermediate time point analyses and phase B of the study demonstrate evidence of the efficacy of THC/CBD spray with both the primary and certain secondary endpoints showing a significant difference in favor of THC/CBD spray. These apparently paradoxical results make the interpretation of this study difficult.

The overall response of patients in phase A was good, both to active and placebo medication. In published studies of THC/CBD spray in neuropathic pain to date, this is the largest placebo effect described by a substantial margin [20–24]. At week 10 of this 14-week study, the proportion of patients in the THC/CBD spray group who achieved at least a 30 % improvement from baseline in mean pain NRS score was significantly greater than on placebo, reflecting the fact that new placebo responses occurred in the final weeks of treatment, while the effect with THC/CBD spray remained steady. Consistent with two previously reported GW studies, the placebo response appears to be related to dosing design, whereby patients were able to self-administer the oral spray at will, up to a maximum permitted daily dose. This was originally intended to reflect as far as possible the "real-world" use of THC/CBD spray, whereby patients initially experiment with dosing to find their optimum dose level and which, once established, is usually maintained thereafter. However, the consequence of allowing patients to determine their own dose was that those on placebo took significantly more doses than those on the THC/CBD spray, potentially confounding the comparison between treatment groups. Placebo group patients who titrated to the maximum dose had disproportionate improvements in pain scores, and a number of these patients reached the maximum permitted dose as the study period was drawing to a close. Self-titration combined with a subjective endpoint seems therefore to have significantly impacted the placebo response. Other recent studies also report high placebo response rates, and rates appear to be growing in clinical research in general [25, 26].

In an attempt to identify any subgroup of patients who may have been responsible for this finding in phase A of the study, we carried out a number of unplanned, post hoc analyses. As might be predicted from the observation that patients on placebo took a greater number of daily sprays, when the groups were balanced for daily sprays, the THC/CBD spray group showed greater separation from placebo (data not shown). There was no notable difference in the response rates according to gender, MS subtype, or individual neuropathic pain type, but patients with a short history of neuropathic pain (less than 4 years) appeared to respond better than those with a long history of pain. These analyses, being post hoc and unplanned, cannot change the

Table 4 Treatment-related adverse events occurring in at least 3 % of the study population during phase A (A) and phase B (B)

System organ class Preferred term	THC/CBD spray ($n = 167$) *n* (%)	Placebo ($n = 172$) *n* (%)
A		
Total patients with at least one AE	**120 (75)**	**106 (62)**
Ear and labyrinth disorder	**20 (12)**	**9 (5)**
Vertigo	15 (9)	6 (3)
Eye disorder	**7 (4)**	**5 (3)**
Vision blurred	4 (2)	1 (1)
Gastrointestinal disorder	**54 (32)**	**40 (23)**
Nausea	13 (8)	7 (4)
Dry mouth	12 (7)	10 (6)
Diarrhea	7 (4)	5 (3)
Vomiting	5 (3)	5 (3)
General disorders and administration site conditions	**40 (24)**	**30 (17)**
Fatigue	16 (10)	9 (5)
Feeling abnormal	5 (3)	2 (1)
Pain	0	1 (1)
Infections and infestations	**34 (20)**	**27 (16)**
Musculoskeletal and connective tissue disorders	**17 (10)**	**20 (12)**
Pain in extremity	0	1 (1)
Muscular weakness	1 (1)	1 (1)
Nervous system disorders	**73 (44)**	**51 (30)**
Dizziness	34 (20)	7 (4)
Somnolence	16 (10)	3 (2)
Headache	7 (4)	6 (3)
Disturbance in attention	6 (4)	1 (1)
Dysgeusia	6 (4)	1 (1)
Memory impairment	6 (4)	1 (1)
Balance disorder	5 (3)	2 (1)
Psychomotor skills impaired	5 (3)	0
Neuralgia	1 (1)	1 (1)
Psychiatric disorders	**27 (16)**	**12 (7)**
Depression	2 (1)	0
Respiratory, thoracic, and mediastinal disorders	**8 (5)**	**11 (6)**
Pharyngolaryngeal pain	2 (1)	1 (1)

System organ class Preferred term	Open-label		Randomized-withdrawal	
	THC/CBD spray ($n = 21$) *n* (%)	Placebo ($n = 37$) *n* (%)	THC/CBD spray ($n = 21$) *n* (%)	Placebo ($n = 21$) *n* (%)
B				
Total patients with at least one AE	**8 (38)**	**18 (49)**	**2 (10)**	**5 (24)**
Cardiac disorders	**0**	**1 (3)**	**0**	**0**
Ear and labyrinth disorders	**1 (5)**	**7 (19)**	**0**	**0**
Vertigo	1 (5)	7 (19)	0	0
Gastrointestinal disorders	**1 (5)**	**3 (8)**	**0**	**0**
Paraesthesia oral	1 (5)	0	0	0
Diarrhea	0	1 (3)	0	0
Dry mouth	0	1 (3)	0	0

Table 4 continued

System organ class Preferred term	Open-label		Randomized-withdrawal	
	THC/CBD spray ($n = 21$) *n* (%)	Placebo ($n = 37$) *n* (%)	THC/CBD spray ($n = 21$) *n* (%)	Placebo ($n = 21$) *n* (%)
Hypoaesthesia oral	0	1 (3)	0	0
Nausea	0	1 (3)	0	0
Vomiting	0	1 (3)	0	0
General disorders and administration site conditions	**1 (5)**	**4 (11)**	**1 (5)**	**0**
Fatigue	1 (5)	2 (5)	0	0
Feeling drunk	0	1 (3)	0	0
Mucosal erosion	0	0	1 (5)	0
Hepatobiliary disorders	**0**	**1 (3)**	**0**	**0**
Infections and infestations	**1 (5)**	**3 (8)**	**0**	**0**
Investigations	**0**	**0**	**0**	**1 (5)**
Hepatic enzyme increased	0	0	0	1 (5)
Musculoskeletal and connective tissue disorders	**0**	**2 (5)**	**0**	**1 (5)**
Pain in extremity	0	1 (3)	0	0
Nervous system disorders	**2 (10)**	**8 (22)**	**0**	**2 (10)**
Ageusia	0	1 (3)	0	0
Cognitive disorder	0	1 (3)	0	0
Dysarthria	0	1 (3)	0	0
Headache	0	1 (3)	0	0
Hypersomnia	1 (5)	0	0	0
Monoparesis	0	1 (3)	0	0
Quadriparesis	0	1 (3)	0	0
Somnolence	0	2 (5)	0	0
Tremor	0	1 (3)	0	0
Psychiatric disorders	**2 (10)**	**1 (3)**	**1 (5)**	**1 (5)**
Depression	0	0	1 (5)	0
Insomnia	1 (5)	0	0	1 (5)
Reproductive system and breast disorders	**1 (5)**	**0**	**0**	**0**
Skin and subcutaneous tissue disorders	**1 (5)**	**0**	**0**	**1 (5)**
Dry skin	0	0	0	1 (5)

MS multiple sclerosis. *Bold items* indicate the total numbers of patients with an AE by System Organ Class (SOC) according to the MedDRA classification of AEs

conclusion that phase A of this study failed to show a significant difference between THC/CBD spray and placebo, but they may help to inform the design of future studies. The subgroup analyses suggest that patients with a long history of refractory pain may be less likely to respond—a conclusion that may seem intuitive, but is supported by the post hoc analyses of phase A of this study.

In contrast to phase A, patients in phase B were instructed to remain on a stable daily dose of study medication. In this case, THC/CBD spray demonstrated an analgesic effect, with time to withdrawal being significantly longer in the THC/CBD spray treatment group. Thus, it is important to ensure that patients in placebo-controlled studies take a balanced number of daily doses of study medication in relation to the active treatment, which is something to consider in the design of future studies.

The primary efficacy endpoint of time to treatment failure in phase B was in favor of the THC/CBD spray, with significantly more patients from the placebo group failing treatment compared with patients randomized to the THC/CBD spray. Moreover, the results of all other symptom-related endpoints showed that THC/CBD spray patients maintained or improved their response whilst the symptoms of those who switched from THC/CBD spray to placebo worsened in the 4 weeks following cessation of active treatment.

The European Medicines Agency guidelines acknowledge that patients with severe pain, especially if previously

treated, may not respond to new therapies. Considering that the average duration of pain in this study was in excess of 5 years, and many patients had failed to respond adequately to previous medications, the patients investigated here represented an especially resistant treatment group [27]. The fact that more than half of the patients who received THC/CBD spray in phase A experienced at least a 30 % reduction in pain is, therefore, encouraging; however, the large placebo response somewhat confounds this finding. It is also reassuring that patients receiving THC/CBD spray reported an analgesic effect in phase B of this study.

As well as the demonstrated placebo effect, the conventional parallel-group, placebo-controlled, randomized study design used in phase A could also have impacted the findings from this study. This approach only provides information about the average response to treatment, and includes results for subjects who do not respond to treatment. In a population with a high proportion of nonresponders, such as may occur in chronic refractory neuropathic pain, it may simply be the case that any genuine differences between drug and placebo are masked by the high rate of nonresponders. If this happens, the results may not tell us much about the effectiveness of the medicine in a clinical setting, where patients who fail to respond would not usually continue treatment. In 2008, McQuay et al. [28] concluded that the enriched enrolment randomized-withdrawal (EERW) design, rather than the conventional design, is potentially valuable in addressing this question, and should be considered especially in the study of chronic pain to avoid the false conclusion of lack of efficacy. Phase B of this study incorporated an EERW design and the efficacy findings were statistically significant in favor of THC/CBD spray. The randomized-withdrawal from THC/CBD spray precipitated a worsening in the majority of the outcome measures, while maintenance of effect of THC/CBD spray was demonstrated. The results from phase B support the proposal that the efficacy of THC/CBD spray is maintained in long-term use.

In terms of safety, it was found that the THC/CBD spray was generally well tolerated in this study, with the majority of AEs considered to be mild to moderate in severity. Three patients in the THC/CBD spray arm and two in the placebo arm experienced a treatment-related SAE. The majority of AEs had resolved by the end of the study. There was no evidence of a withdrawal syndrome in those patients who stopped THC/CBD spray, despite a prolonged period on the medicine.

In summary, we found that in this treatment-resistant population, the THC/CBD spray showed a high response rate, statistically different to placebo at week 10 but not at the week 14 primary endpoint in phase A. Randomized-withdrawal from THC/CBD spray precipitated a significant deterioration in pain scores in the placebo group, while maintenance of effect with THC/CBD spray was demonstrated both for the primary outcome measure of time to treatment failure, and for the key pain-related secondary measures of sleep and mean pain scores. We conclude that this study has provided further results useful for determining the efficacy of THC/CBD spray in the treatment of CNP due to MS. The results support previously published proposals that an EERW study design may be of particular value in identifying clinically relevant responses in this patient population, and suggest that future studies may benefit from the incorporation of a balanced dosing regimen between the different arms of the study.

Trial Information The ClinTrials.gov Trial Number for this study is NCT00391079.

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Conflicts of interest R. Langford, J. Mares, A. Novotna, M. Vachora, I. Novakova, W. Notcutt, and S. Ratcliffe were all investigators in this study and their organizations received investigator fees from GW Pharma Ltd. accordingly for their participation in the study. R. Langford, W. Notcutt, and S. Ratcliffe have received consultancy and speaker fees from GW Pharma Ltd. to attend meetings.

Ethical standard All human studies must state that they have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsenki.

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