J Neurol (2015) 262:27–40
DOI 10.1007/s00415-014-7502-9

ORIGINAL COMMUNICATION

A multicentre, open-label, follow-on study to assess the long-term maintenance of effect, tolerance and safety of THC/CBD oromucosal spray in the management of neuropathic pain

B. Hoggart · S. Ratcliffe · E. Ehler · K. H. Simpson · J. Hovorka · J. Lejčko · L. Taylor · H. Lauder · M. Serpell

Received: 5 August 2014 / Revised: 9 September 2014 / Accepted: 10 September 2014 / Published online: 30 September 2014

Abstract Peripheral neuropathic pain (PNP) poses a significant clinical challenge. The long-term efficacy of delta-9-tetrahydrocannabinol (THC)/cannabidiol (CBD) oromucosal spray was investigated in this 38-week open-label extension study. In total, 380 patients with PNP associated with diabetes or allodynia entered this study from two parent randomised, controlled trials. Patients received THC/CBD spray for a further 38 weeks in addition to their current analgesic therapy. Neuropathic pain severity was the primary efficacy measure using a pain 0–10 numerical rating scale (NRS). Additional efficacy, safety and tolerability outcomes were also investigated. In total, 234 patients completed the study (62 %). The pain NRS showed a decrease in score over time in patients from a mean of 6.9 points (baseline in the parent studies) to a mean of 4.2 points (end of open-label follow-up). The proportion of patients who reported at least a clinically relevant 30 % improvement in pain continued to increase with time (up to 9 months); at least half of all patients reported a 30 % improvement at all time points. Improvements were observed for all secondary efficacy outcomes, including sleep quality 0–10 NRS scores, neuropathic pain scale scores, subject global impression of change and EQ-5D questionnaire scores. THC/CBD spray was well tolerated for the study duration and patients did not seek to increase their dose with time, with no new safety concerns arising from long-term use. In this previously difficult to manage patient population, THC/CBD spray was beneficial for the majority of patients with PNP associated with diabetes or allodynia.

Keywords Cannabidiol · Cannabinoid · Delta-9-tetrahydrocannabinol · Neuropathic pain · THC/CBD spray

Introduction

Neuropathic pain is a chronic, debilitating condition with an estimated prevalence of over 1 % in the general US population [1]. It can be triggered by a variety of conditions, but the mechanisms of developing neuropathic pain are specific to the damage and/or dysfunction of the nervous system and are not necessarily related to the underlying disease. It has therefore been suggested that the optimal approach to neuropathic pain

B. Hoggart (✉)
Pain Management Research, Solihull Hospital, Solihull, UK
e-mail: wallisb98@gmail.com;
barbara.hoggart@heartofengland.nhs.uk

S. Ratcliffe
MAC Clinical Research, Trafford Park, Manchester, UK

E. Ehler
Neurologické odd., Krajská nemocnice Pardubice,
53203 Pardubice, Czech Republic

K. H. Simpson
Pain Management Services, Seacroft Hospital, York Road,
Leeds, UK

J. Hovorka
Neurologické odd., Nemocnice Na Františku s poliklinikou,
110 00 Prague 1, Czech Republic

J. Lejčko
Centrum pro léčbu bolesti, Fakultní nemocnice,
304 60 Plzeň - Lochotín, Czech Republic

L. Taylor · H. Lauder
GW Pharma Ltd, Porton Down Science Park, Salisbury,
Wiltshire, UK

M. Serpell
Pain Clinic Office, Gartnavel General Hospital, 1053 Great
Western Road, Glasgow, UK

management should be based on the mechanism(s) underlying the pain, rather than the disease which triggers the neuropathic events [2, 3]. However, many patients achieve only partial pain relief despite management with analgesic agents. Thus, there is still a clear unmet need for this group of patients.

The endocannabinoid system modulator, Δ^9-tetrahydrocannabinol (THC)/cannabidiol (CBD) oromucosal spray (Sativex®), is formulated from plant extracts prepared from genetically distinct chemotypes of *Cannabis sativa* L. These cannabis plants contain cannabinoids, which act primarily via specific cannabinoid receptors designated CB_1 and CB_2 [4]. CB_1 receptors are predominantly found in the central nervous system, while CB_2 receptors are located primarily in the periphery, including the immune system [4].

The two most relevant cannabinoids in this product are THC and CBD, contained in the spray at an approximate 1:1 ratio with smaller amounts of other cannabinoids, flavonoids and terpenes [5]. It has been recently licenced for use in various European countries for the relief of spasticity in multiple sclerosis (MS) [6], as well as outside the European Union. THC/CBD spray is also licenced for use in Canada for the management of central neuropathic pain (CNP) in MS.

THC and CBD have analgesic effects in numerous animal models of pain [7–10]. Previous clinical studies using synthetic THC or a synthetic metabolite of THC demonstrated effects in patients with CNP [11] and peripheral neuropathic pain (PNP) associated with allodynia [12], respectively. In a randomised controlled trial (RCT), THC/CBD spray showed analgesic effects in CNP associated with MS [13, 14], as well as in pain following brachial plexus avulsion [15]. A further study concluded that THC/CBD spray provided a clinically relevant improvement in PNP associated with allodynia [16].

Two parent RCTs preceded the current study [17, 18]. Both showed the ability of THC/CBD spray to alleviate pain in patients with PNP associated with diabetes mellitus or allodynia (i.e., different underlying pathologies). However, there was a need to investigate the long-term efficacy, safety and tolerability of THC/CBD spray in this indication. This 9-month open-label, follow-on study was therefore designed and performed in accordance with the guidance notes for the clinical development of new medicinal products in neuropathic pain, compiled by Committee for Medicinal Products for Human Use (CHMP) [19].

Methods

Study design

The study comprised 38 weeks of open-label THC/CBD spray treatment, following the original clinical trials treatment period, at 66 study sites (38 centres in the United Kingdom, 15 in the Czech Republic, 8 in Romania, four in Belgium and one in Canada). Patients with allodynia or PNP associated with diabetes who had received THC/CBD spray or placebo in one of two parent RCTs were invited to take part in the study. At this study extension baseline visit (visit 1 of 6), the following information was recorded: eligibility, informed consent, medical history, physical examination, 12-lead electrocardiogram (ECG), pain 0–10 numerical rating scale (NRS) and adverse events (AEs). Further study visits took place at weeks 2, 14, 26 and 38, with an end of study visit 28 days following study completion or withdrawal. At each subsequent study visit, the following information was recorded: concomitant medications, vital signs, AEs, oral examination, intoxication 0–10 NRS, neuropathic pain scale (NPS) score and sleep quality 0–10 NRS score. Patients also completed a daily dosing diary and a weekly symptom diary recording the severity of their neuropathic pain using a pain 0–10 NRS. At week 38 the following further information was recorded: subject global impression of change (SGIC) and EQ-5D lifestyle questionnaires, clinical laboratory sampling and a pregnancy test for female patients.

Inclusion and exclusion criteria

Main inclusion criteria

Eligible patients had participated in, completed and complied with all the study requirements of one of the above-mentioned parent RCTs [17, 18] and had completed the parent study within the last 7 days. Eligible patients showed tolerability to the study medication (THC/CBD spray or placebo) in the parent RCTs and were expected to gain clinical benefit from receiving THC/CBD in the opinion of the investigator. Furthermore, they had to be willing to comply with the study protocol procedures and agree for the responsible authorities (i.e., primary care physician or hospital consultant) to be notified of their participation in the study.

Exclusion criteria

The exclusion criteria of the previous RCTs were re-checked. These included exclusion of patients with a concurrent history of severe psychiatric, convulsive, renal, hepatic or cardiovascular disorders, or those with a history of alcohol or substance abuse. Those with a known or suspected hypersensitivity to cannabis or cannabinoid-based medications were excluded. Females of child-bearing age, or males with partners of child-bearing age were also excluded, unless willing to ensure that adequate contraception was used for the study duration and for 3 months

thereafter. Pregnant or lactating females were excluded, as were patients who had received any investigational medicinal product within 12 weeks of study commencement (with the exception of THC/CBD spray taken during the preceding RCTs). Patients with any physical abnormalities or a disease (in the opinion of the investigator) which could compromise their safety during the study were excluded, as were those who had been previously randomised into this open-label extension study, as well as those intending to donate blood during the study (for safety reasons).

Treatment and dosing

A pump action oromucosal spray was used to deliver study medication. Each 100 μL actuation of THC/CBD spray delivered 2.7 mg of THC and 2.5 mg of CBD to the oral mucosa. Patients were restricted to a maximum of eight sprays per 3 h period and 24 actuations every 24 h. A 2-week titration period to allow for dosing optimisation began at study visit 2 (on day 14). During the baseline period patients self-titrated, titrating upwards by up to 50 % of the previous day's dose to reach their optimal dose depending on efficacy, tolerability and maximum permitted dose.

Concomitant medication

Due to the long-term nature of the study, investigators were allowed to prescribe medications or other managements to provide adequate supportive care if the patient's condition required, provided the inclusion and exclusion criteria were not compromised. Sites were advised to proceed with caution when co-administering any drugs exhibiting significant metabolites, inhibitors or activators of cytochrome P450 3A isoenzymes, due to the potential interaction with cannabis-based medicines.

Prohibited medication

Patients were required to abstain from using any herbal cannabis or cannabinoids other than THC/CBD spray for the entire study duration.

Study endpoints

Primary efficacy endpoints

The primary efficacy endpoint was the change in pain severity, defined as the change from the parent RCT baseline to the end of open-label treatment in pain 0–10 point NRS scores. The pain 0–10 NRS was recorded by patients weekly on a selected nominated day in their diary books. The question posed differed slightly depending on which parent RCT the patient had participated in. Patients with allodynia were asked: "On a scale of '0–10' please indicate the average level of your nerve pain over the last 7 days", while patients with diabetic neuropathy were asked: "On a scale of '0–10' please indicate the average level of your nerve pain due to diabetes over the last 7 days". The anchors for both questions were: 0 = 'no pain' and 10 = 'worst possible pain'. Patients were instructed to relate 'no pain' to the time prior to the onset of their neuropathic pain. The proportion of responders with an equal to or greater than 30 or 50 % improvement in the level of pain experienced was a co-primary endpoint of this study.

Secondary efficacy endpoints

Other efficacy endpoints were THC/CBD spray daily dose, NPS score, sleep quality 0–10 NRS score, intoxication 0–10 NRS score and SGIC and quality of life EQ-5D health questionnaire outcomes.

NPS

The NPS (neuropathic pain scale PDF [17, 20]) was collected at the pre-treatment baseline and the final visit of the parent RCTs and at each of the open-label extension study visits (end of weeks 2, 14, 26 and 38). The main variable for analysis was NPS score at each visit, which was summarised by parent RCTs and overall, using descriptive statistics at each time point. Summaries of the changes from the pre-treatment baseline of the parent RCTs were produced.

Sleep quality 0–10 NRS

The sleep quality 0–10 NRS score was collected at the pre-treatment baseline and the final visit of the parent RCTs and at each of the open-label extension study visits (end of weeks 2, 14, 26 and 38). Patients were asked, "On a scale of '0–10', 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)'. The main variable for analysis was the sleep quality 0–10 NRS score at each visit, which was summarised by parent RCTs and overall, using descriptive statistics at each time point.

Intoxication 0–10 NRS

The intoxication 0–10 NRS score was collected at the pre-treatment baseline and the final visit of the parent RCTs and at each of the open-label extension study visits (end of

weeks 2, 14, 26 and 38). Patients were asked how intoxicated they felt, with the anchors: 0 = 'no intoxication' and 10 = 'extreme intoxication'. The main variable for analysis was the intoxication 0–10 NRS score at each visit, which was summarised by parent RCTs and overall, using descriptive statistics at each time point.

SGIC

The SGIC was collected at the end of open-label study (completion or withdrawal) only. A 7-point Likert-type scale was used to evaluate the patients perception of their nerve pain with the anchors: 'very much improved', 'much improved', 'slightly improved', 'no change', 'slightly worse', 'much worse' or 'very much worse'.

Eq-5D

The EQ-5D questionnaire (see [17]) was completed at pre-treatment baseline and at the final visit of the parent RCTs, as well as at the end of open-label extension study (completion or withdrawal). The weighted health state index 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). Both weighted health state index and self-rated health status were summarised by parent RCTs and overall at the three time points using descriptive summary statistics. Summaries of the changes from the pre-treatment baseline of the parent RCTs were produced.

In addition, the five EQ-5D descriptive system questions (mobility, activity, self-care, pain, anxiety) were summarised by parent RCTs and overall as shift tables from the pre-treatment baseline of the parent RCTs to end of the open-label extension study (completion or withdrawal).

Safety endpoints

The safety endpoints of the study included the incidence of AEs, laboratory parameters, vital signs and ECG results.

Statistical methods

There was no formal sample size for the study. Patients who had participated in the two parent RCTs to investigate neuropathic pain were considered for enrolment into the current study. As the study was non-comparative, no formal hypothesis testing was performed. The statistics are descriptive only.

Amendments during the trial

During the course of the study, one amendment affecting the open-label extension study was implemented and approved by the Multi Centre Research Ethics Committee, Ethical Committees and competent authorities. The amendment relaxed an entry criterion related to glycosylated haemoglobin, sinus bradycardia and creatinine clearance to allow some patients that had safely completed the parent RCTs to enter the extension study. Following the growing tolerability and safety evidence on Sativex, the blood glucose test was removed from the list of biochemistry tests to be performed. There were also minor corrections to the study medication-dosing regimen on the first 2 days of dosing, which was inconsistent with the parent studies, and other instructions given to the patients.

Results

This open-label extension study took place between 18 October 2005 and 15 June 2007. A full summary breakdown of all patients enrolled is shown in Fig. 1. In the parent RCT, which looked at PNP associated with allodynia, 246 patients were randomised and 173 (70 %) completed the study [17]. In the parent RCT, which involved PNP associated with diabetes, 298 patients were randomised and 230 (77 %) completed the study [18]. 21 patients in the allodynia RCT and 15 patients in the diabetes RCT, who terminated study treatment prematurely but completed all study procedures, were also eligible for the open-label extension study. This was a total of 439 completers within the two studies. There were 57 patients (13 %) who were eligible, but elected not to continue into the open-label extension. While the reasons for this were not captured during the study, the vast majority was simply down to the patient's choice. This left a total of 382 patients who were screened for the open-label extension study, of these 166 patients had previously been taking THC/CBD spray (mean daily doses: allodynia RCT = 8.9 sprays per day; diabetic neuropathy RCT = 9.5 sprays per day) and 216 had been taking placebo (mean daily doses: allodynia RCT = 14.2 sprays per day; diabetic neuropathy RCT = 13.8 sprays per day). Study population demographics are presented in Table 1. The overall mean duration of PNP in these patients at enrolment was 5.4 years and was similar between the patients from both the parent RCTs. THC/CBD was used for 94 % of days in the open-label extension study; the median use was 249 days. From month 1 to month 9, the median daily dose of THC/CBD spray was 6.0–8.0 actuations.

Study withdrawals occurred throughout the open-label extension study with no notable difference in the time to withdrawal for either previous treatment group. However, 27 % of patients who had received placebo in the parent RCTs withdrew from the extension study due to AEs compared with 11 % who had received THC/CBD spray.

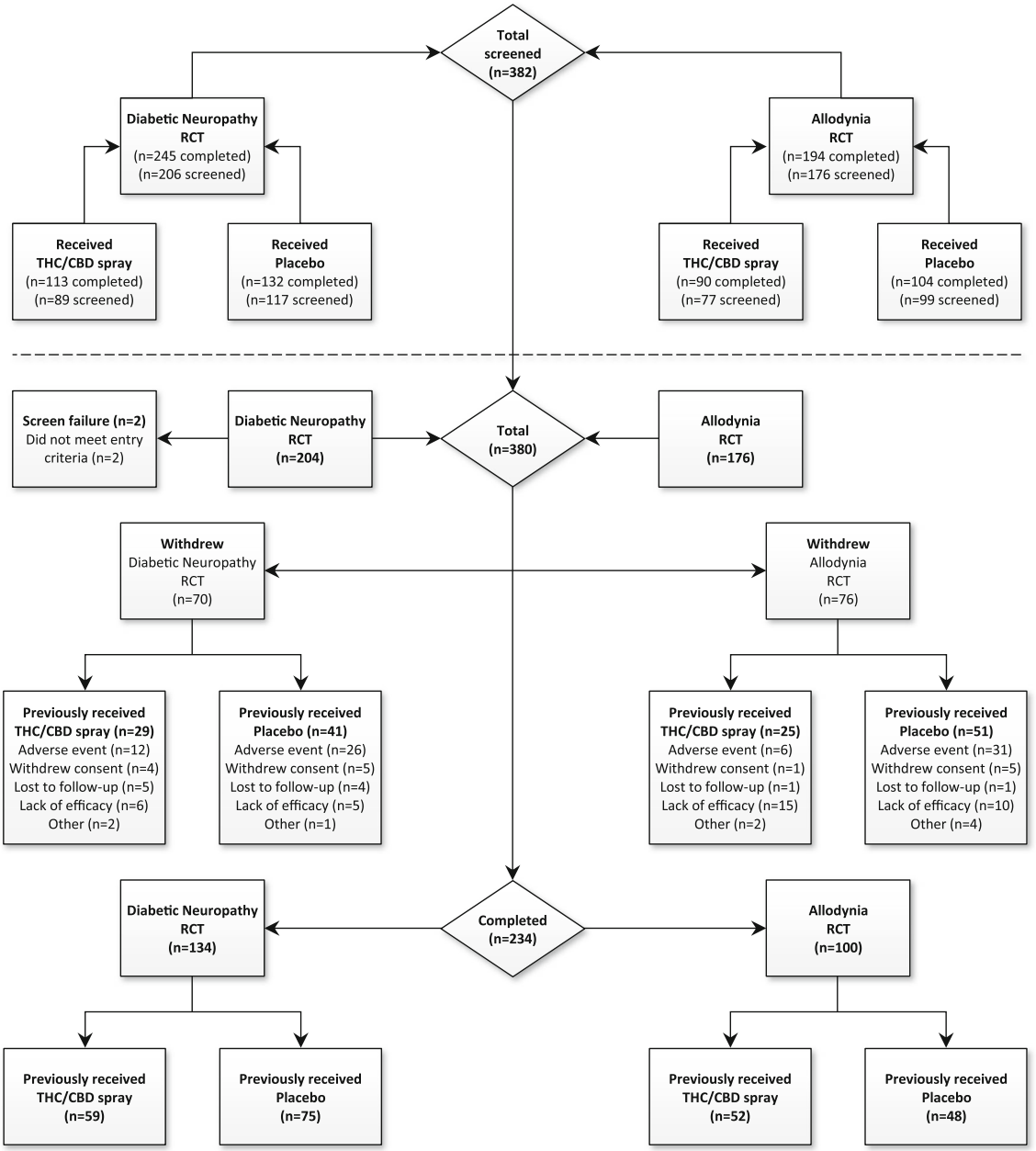

Fig. 1 Disposition of patients

13 % of patients who had received THC/CBD spray in the parent RCTs withdrew from the extension study due to a lack of efficacy compared with 7 % who had received placebo.

Concomitant medication

Concomitant analgesic medication was used by 84 % of patients, many of whom were receiving polypharmacy for pain management. A summary of concomitant medications used during the study is presented in Table 2. The most common analgesics taken at baseline were anticonvulsants, tricyclic anti-depressants, opioids and non-steroidal anti-inflammatory drugs (NSAIDs). The most commonly used non-analgesic concomitant medications were HMG-CoA reductase inhibitors (38 %), ACE inhibitors (35 %), biguanides (29 %) and platelet aggregation inhibitors (25 %).

Eighty-nine percent of patients had a history of previously trying and failing at least one analgesic for their PNP; the two most common being anticonvulsants and NSAIDs.

Table 1 Demographics, baseline characteristics and underlying reason for peripheral neuropathic pain (PNP) by parent randomised control trial (RCT)

Patient demographics and baseline characteristics by parent RCT			
Demographic/characteristic	No. of patients (%)		
	Diabetic neuropathy RCT ($n = 204$)	Allodynia RCT ($n = 176$)	Combined ($n = 380$)
Gender			
Male	122 (60)	78 (44)	200 (53)
Female	82 (40)	98 (56)	180 (47)
Ethnic origin			
White/Caucasian	200 (98)	174 (99)	374 (98)
Black/African American	1 (<0.5)	1 (1)	2 (1)
Hispanic/Latino	1 (<0.5)	0	1 (<0.5)
Asian	2 (1)	0	2 (1)
Others[a]	0	1 (1)	1 (<0.5)
Previous cannabis use (at any time, prior to parent RCTs)	21 (10)	17 (10)	38 (10)
Demographic/characteristic	Mean (SD)		
	Diabetic neuropathy RCT ($n = 204$)	Allodynia RCT ($n = 176$)	Combined ($n = 380$)
Age (years)	59.1 (10.04)	56.3 (13.88)	57.8 (12.03)
Body mass index (kg/m^2)	31.7 (6.95)	27.7 (5.85)	29.9 (6.76)
Duration of any underlying condition causing peripheral neuropathic pain (PNP) (years)	12.29 (8.83)	6.54 (6.82)	9.63 (8.46)
Duration of PNP due to underlying condition (years)	4.99 (4.27)	5.77 (6.27)	5.35 (5.30)

Type of underlying condition causing PNP by parent RCT	No. of patients (%)		
Condition	Diabetic neuropathy RCT ($n = 204$)	Allodynia RCT ($n = 176$)	Combined ($n = 380$)
Focal nerve lesion	–	69 (39)	69 (18)
Peripheral neuropathy	–	46 (26)	46 (12)
Post-herpetic neuralgia	–	40 (23)	40 (11)
Complex regional pain syndrome type 2	–	25 (14)	25 (7)
Diabetes mellitus	204 (100)	–	204 (54)

[a] The patient of "other" ethnic origin was of Chinese/English mixed race

Efficacy results

Pain 0–10 NRS

All patients showed an improvement in pain 0–10 NRS score over the initial weeks of treatment and there was subsequent maintenance of analgesia over time (Fig. 2). The parent RCT data are shown in Table 3. The baseline for the combined parent studies was a mean of 6.9 points that had decreased to 5.5 points by the end of the parent RCTs. This improvement continued with time in the current study. At month 9 that was the end of open-label treatment, the mean pain 0–10 NRS score had reduced further to 4.2 points in the remaining patients (Fig. 2). Moreover, this improvement was observed over a stable background of concomitant analgesic therapy throughout the 9 months of assessment (Table 2). The mean pain score of patients who had previously received placebo during the parent RCTs decreased by 1.4 points over the 9 months of this extension study when they received THC/CBD spray (Table 3).

Table 2 Summary of concomitant analgesic and non-analgesic medications taken by ≥5 % of all patients during the study and by parent randomised controlled trial (RCT)

Number of analgesic medications taken by parent RCT			
Analgesics taken	No. of patients (%)		
	Diabetic neuropathy RCT ($n = 204$)	Allodynia RCT ($n = 176$)	Combined ($n = 380$)
0	47 (23)	12 (7)	59 (16)
≥1	157 (77)	164 (93)	321 (84)
≥2	117 (57)	122 (69)	239 (63)
≥3	66 (32)	84 (48)	150 (39)
≥4	41 (20)	53 (30)	94 (25)

Analgesic medications taken at the start and end of the study		
Analgesic type	No. of patients (total %)	
	Study onset	End of study
Anticonvulsants[a]	167 (44)	173 (46)
Tricyclic anti-depressants[b]	133 (35)	131 (34)
Non-steroidal anti-inflammatories[c]	118 (31)	118 (31)
Other opioids[d]	118 (31)	123 (32)
Other analgesics[e]	88 (23)	97 (26)
Strong opioids[f]	56 (15)	57 (15)

Non-analgesic medications taken during the study by parent RCT			
Non-analgesics	No. of patients (%)		
	Diabetic neuropathy RCT ($n = 204$)	Allodynia RCT ($n = 176$)	Combined ($n = 380$)
HMG CoA reductase inhibitors	120 (59)	25 (14)	145 (38)
ACE inhibitors	111 (54)	23 (13)	134 (35)
Biguanides	108 (53)	4 (2)	112 (29)
Platelet aggregation inhibitors (excl. Heparin)	79 (39)	16 (9)	95 (25)
Fast-acting insulins and analogues	84 (41)	1 (1)	85 (22)
Proton pump inhibitors	46 (23)	38 (22)	84 (22)
Selective beta (β) blocking agents	55 (27)	20 (11)	75 (20)
Sulfonamides	54 (26)	10 (6)	64 (17)
Dihydropyridine derivatives	47 (23)	14 (8)	61 (16)
Sulfonamides, urea derivatives	56 (27)	3 (2)	59 (16)
Angiotensin II antagonists, plain	36 (18)	11 (6)	47 (12)
Thiazides, plain	30 (15)	11 (6)	41 (11)
Intermediate-acting insulins and analogues	40 (20)	0	40 (11)
Long-acting insulins and analogues	40 (20)	0	40 (11)
Glucocorticoids	17 (8)	18 (10)	35 (9)
Thyroid hormones	15 (7)	17 (10)	32 (8)
Intermediate-acting insulins and analogues (combined with fast-acting)	31 (15)	0	31 (8)
Selective β-2 adrenoreceptor agonists	15 (7)	16 (9)	31 (8)
Organic nitrates	24 (12)	6 (3)	30 (8)
Alpha-adrenoreceptor antagonists	15 (7)	8 (5)	23 (6)
Fibrates	20 (10)	3 (2)	23 (6)
Osmotically acting laxatives	9 (4)	13 (7)	22 (6)
Penicillins with extended spectrums	13 (6)	8 (5)	21 (6)
Heparin group	17 (8)	3 (2)	20 (5)
Propulsives	13 (6)	6 (3)	19 (5)

Examples of analgesics included in each class [a] Gabapentin, [b] Amitriptyline, [c] Diclofenac, [d] Codeine, [e] Paracetamol and [f] Morphine

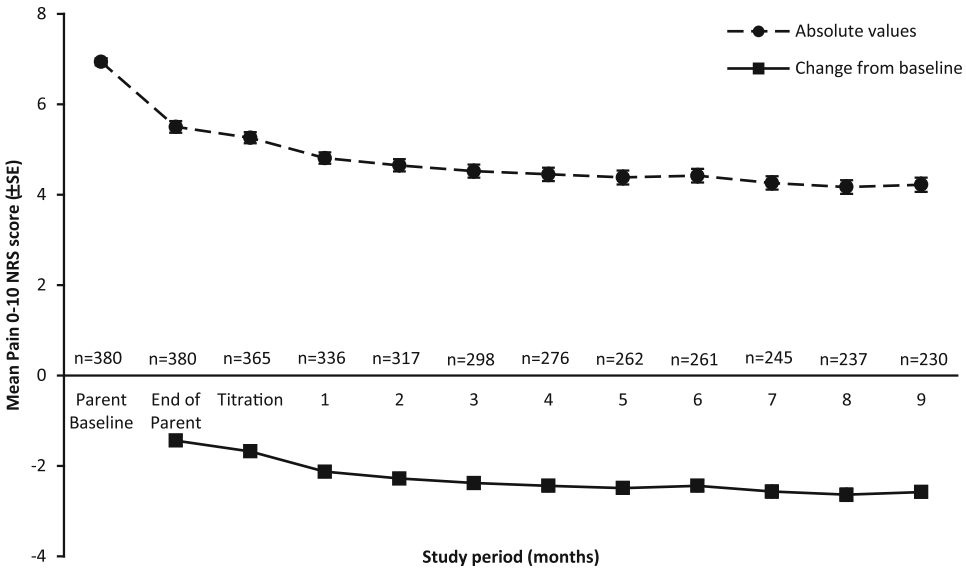

Fig. 2 Patient diary pain 0–10 NRS scores by time (combined patients)

Table 3 Pain 0–10 numerical rating scale scores and new responders at the 30 % improvement level by previous treatment in parent randomised controlled trial (RCT)

Diary pain 0–10 numerical rating scale scores by time and previous treatment in parent RCT												
Study period	Diabetic neuropathy				Allodynia				Combined			
	THC/CBD spray		Placebo		THC/CBD spray		Placebo		THC/CBD spray		Placebo	
	n	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)
Baseline parent RCT	88	6.66 (1.69)	116	6.68 (1.57)	77	7.31 (1.60)	99	7.19 (1.42)	165	6.96 (1.67)	215	6.92 (1.52)
Last week of parent RCT	88	4.65 (2.74)	116	5.11 (2.52)	77	5.87 (2.31)	99	6.43 (1.98)	165	5.22 (2.61)	215	5.72 (2.38)
Current study month 1	81	4.12 (2.44)	104	4.32 (2.30)	69	5.16 (2.26)	82	5.81 (1.96)	150	4.60 (2.41)	186	4.98 (2.27)
Current study month 9	58	3.33 (2.05)	73	3.45 (2.15)	50	5.01 (2.34)	49	5.61 (2.21)	108	4.11 (2.34)	122	4.32 (2.41)

New responders at the 30 % level by previous treatment in parent RCT			
Treatment in parent RCT	No. of patients (%)		
	Diabetic neuropathy ($n = 204$)	Allodynia ($n = 176$)	Combined ($n = 380$)
THC/CBD spray	24 (12)	17 (10)	41 (11)
Placebo	37 (18)	29 (16)	66 (17)

Pain improvement at the 30 and 50 % responder level

A meta-analysis of patients with various painful conditions suggested an approximate 30 % improvement in pain as being clinically significant [21]. The proportion of patients who reported at least a 30 % improvement in pain compared to parent RCT baselines increased with time in this study, with at least half of all patients reporting an improvement in pain at all time points (Fig. 3). Additionally, the number of patients who demonstrated a 50 % improvement increased with time, with a minimum of 30 % of patients at the 50 % improvement level at all time points (Fig. 3). A total of 107 patients (28 % of total) were new responders at the 30 % level of improvement. Of these, 46 (12 % of total) were from the allodynia RCT and 61 (16 % of total) were from the diabetic neuropathy RCT. More than half of these patients (66 patients; 17 % of total) had previously received placebo in the parent RCTs (Table 3).

Secondary efficacy measures

An improvement in the specific NPS scores from the end of the parent RCTs was sustained for the duration of the study and continued to decrease with time until week 26 (Fig. 4). This improvement was seen across all patient groups

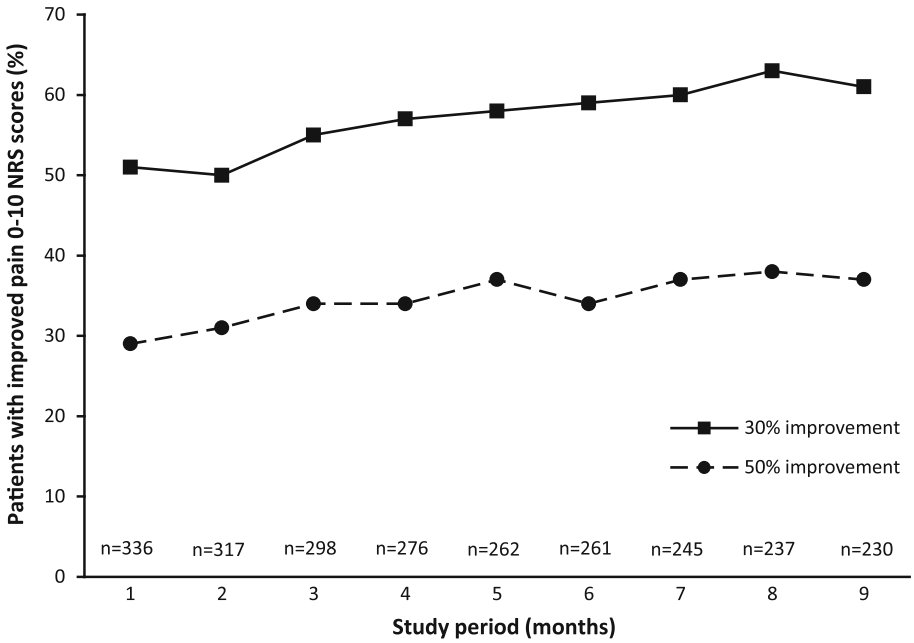

Fig. 3 Pain 0–10 NRS responders at 30 and 50 % improvement by time (combined patients)

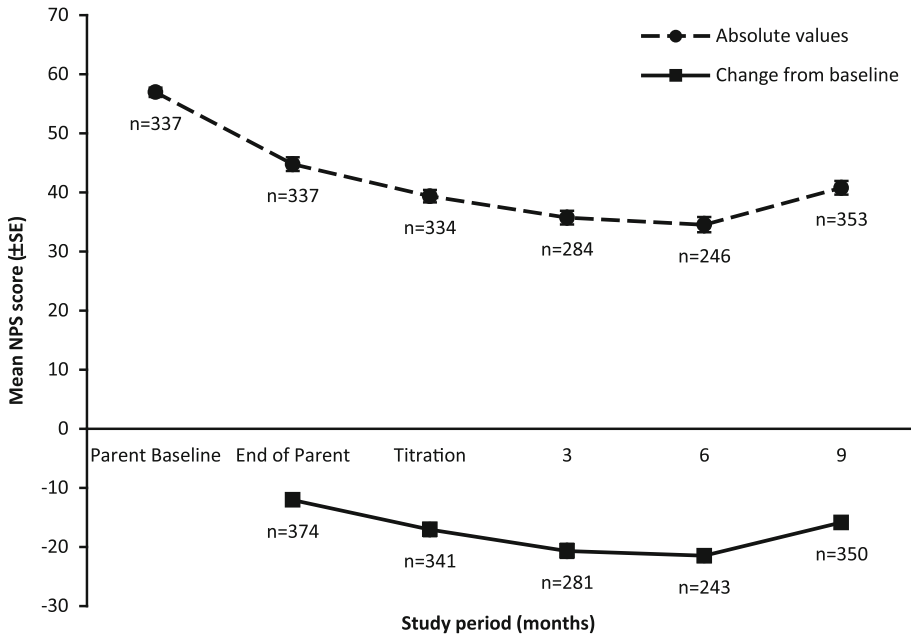

Fig. 4 NPS scores by time (combined patients)

regardless of the type of pain, with a maximum response occurring between 14 and 26 weeks (Fig. 4). The mean NPS total score increased at week 38 (end of treatment) resulting from increased attendance at this visit (94 % attendance at week 38 versus 65 % at week 26). This score therefore gives a better estimate of efficacy and remained an improvement from the end of the parent RCTs.

The summary of responses to treatment at the end of the study in the SGIC analysis is illustrated in Fig. 5. 70 % of patients reported an improvement in nerve pain and only 8 % reported deterioration. 22 % of patients reported no change. Sleep quality 0–10 NRS scores and EQ-5D health questionnaire outcomes, which had improved during the parent RCTs, were maintained for the entire duration of the current study.

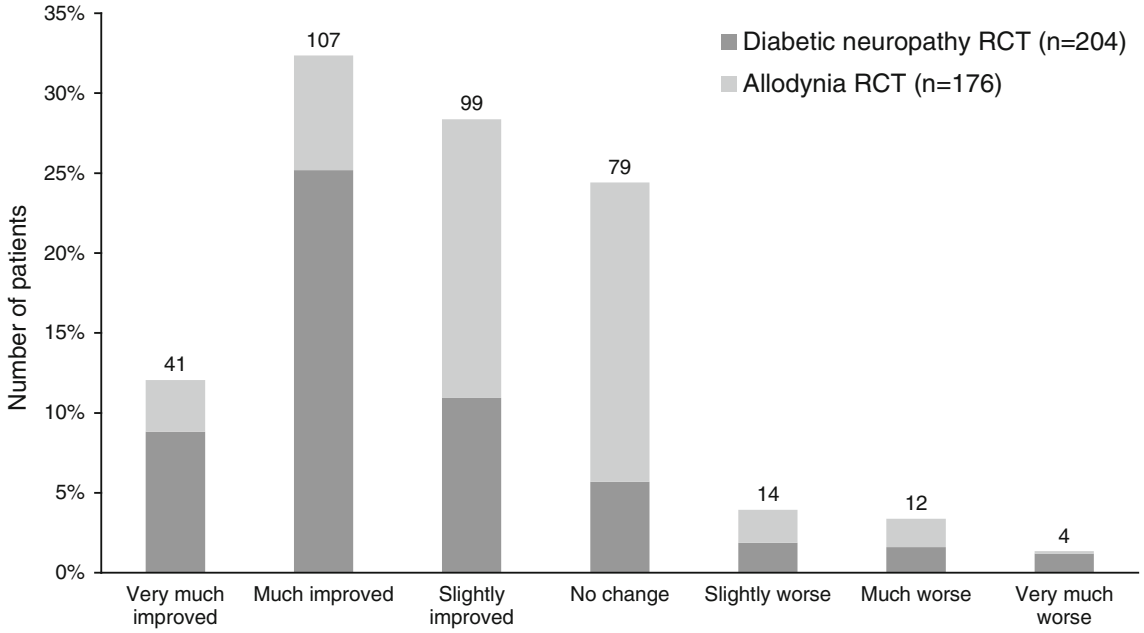

Fig. 5 Subject global impression of change. Total patient numbers for each category are shown above each column

Safety and tolerability

Adverse events

A summary of the most common all-cause and treatment-related AEs with an incidence of 5 % or greater is presented in Table 4. The most common all-cause AEs reported by system organ class (SOC) were nervous system disorders (44 %), gastrointestinal disorders (36 %), general disorders and administration site conditions (24 %), infections and infestations (23 %) and psychiatric disorders (21 %) (Table 4). The only psychiatric disorder with an incidence of 5 % or greater by preferred term was disorientation, experienced by 19 (5 %) of patients.

The most common treatment-related AEs were dizziness (19 %), nausea (9 %), dry mouth (8 %), dysgeusia (7 %), fatigue (7 %), somnolence (7 %) and feeling drunk (6 %). The majority (74 %) of treatment-emergent AEs resolved without sequelae by the end of the study. AEs which were most commonly reported to be continuing at the end of the study were fatigue, dizziness and insomnia.

There were no significant differences in the incidence of AEs reported in relation to the patients' mean daily dose. 77 % in the lower mean dose category (<6.8 actuations per day) reported at least one AE and 78 % in the higher dose category (>6.8 actuations per day) reported at least one AE.

Serious adverse events and deaths

A total of 40 patients (11 %) experienced serious adverse events (SAEs) during the study, with four patients (1 %) experiencing a treatment-related SAE. The prevalent all-cause SAEs reported were in the SOCs of nervous system disorders in ten patients (3 %), infections and infestations in seven patients (2 %), gastrointestinal disorders and general disorders and administration site conditions in five patients (1 %) and cardiac disorders in four patients (1 %). The only SAEs that were considered to be treatment related were in the SOCs of nervous system disorders and psychiatric disorders, with two patients experiencing amnesia, one event of paranoia, and one suicide attempt.

Two deaths were reported during the course of the study. One was from acute pancreatitis and the other from disseminated cancer. Both events were considered to be unrelated to the study medication.

Treatment cessation due to adverse events

Twenty-three percent of patients permanently ceased study medication due to AEs; 7 % due to severe AEs and 18 % due to AEs that were considered to be treatment-related. The majority of these events occurred within the first 7 days of treatment, and were within the SOCs of nervous system disorders and gastrointestinal disorders. Psychiatric AEs that resulted in cessation of study treatment totalled 21 events (5 % of total), 16 of which occurred in patients who had received placebo during the parent RCTs and five in patients who had received THC/CBD spray. Of the 42 patients (11 % of total) who ceased study medication due to nervous system AEs, 28 had previously received placebo in the parent RCT, while 14 had received THC/CBD spray. From the withdrawals due to AEs in the gastrointestinal

Table 4 Most common adverse events (AEs) by primary system organ class and preferred term for patients with at least one AE with an incidence of 5 % or greater by causality

System organ class (SOC)	No. (%) of patients	
Preferred term	All causality	Treatment related
Total patients with at least one adverse event	295 (78)	224 (59)
Nervous system disorders	168 (44)	140 (37)
Dizziness	79 (21)	74 (19)
Dysgeusia	29 (8)	28 (7)
Somnolence	28 (7)	27 (7)
Headache	23 (6)	11 (3)
Gastrointestinal disorders	135 (36)	97 (26)
Nausea	42 (11)	35 (9)
Dry mouth	30 (8)	29 (8)
Vomiting	25 (7)	11 (3)
General disorders and administration site conditions	92 (24)	69 (18)
Fatigue	31 (8)	27 (7)
Feeling drunk	21 (6)	21 (6)
Infections and infestations	89 (23)	9 (2)
Psychiatric disorders	79 (21)	55 (14)
Disorientation	19 (5)	18 (5)
Musculoskeletal and connective tissue disorders	47 (12)	4 (1)
Respiratory, thoracic and mediastinal disorders	43 (11)	16 (4)
Metabolism and nutrition disorders	38 (10)	15 (4)
Injury, poisoning and procedural complications	29 (8)	8 (2)
Vascular disorders	22 (6)	0

disorders SOC (7 % of total), 20 patients had previously received placebo in the parent RCTs and 8 had previously received THC/CBD spray.

Laboratory data and vital signs

The laboratory parameters (biochemistry, haematology and urinalysis) showed no notable trends from baseline and no long-term effects on vital signs were evident.

Intoxication 0–10 NRS

The mean (±SD) baseline intoxication score for the combined parent studies was 0.9 (±2.0) points, which increased to 1.2 (±1.9) points by the end of the parent RCTs. The mean score peaked at 1.9 (±2.3) points following the 2-week titration period and stabilised at 1.5–1.7 (±2.1–2.3) points from 14 weeks onwards. After 9 months of treatment the mean intoxication score was 1.5 (±2.3) points, an increase from baseline of 0.6 (±2.6) points.

Discussion

This study has provided further data to support sustained long-term benefit, safety and tolerability of continued THC/CBD spray use in the management of PNP. Improvements in PNP scores were observed after 4 weeks of treatment with THC/CBD spray and maintained over the 9 months of the study, without an associated increase in daily dose of THC/CBD spray and with no evidence of tolerance developing.

Neuropathic pain is one of the most difficult types of pain to treat [19] and less than half of treated patients receive meaningful benefit with existing drugs, including tricyclic and related anti-depressants, antiepileptic agents and opioids [22]. The population enrolled in this study were diagnosed with neuropathic pain, either secondary to diabetes mellitus or associated with allodynia. They had completed a double-blind RCT of THC/CBD spray for either indication [17, 18]. The majority of patients eligible for this study were already established on a stable dose of regular analgesia (many receiving multiple analgesic medications), but were still experiencing moderate to severe PNP at the onset of the parent RCTs [17, 18].

The population of patients evaluated in this study represented an especially challenging group. The mean duration of PNP was in excess of 5 years and they were largely resistant to existing analgesics. The vast majority reported having tried and failed analgesic therapy in the past. Only a small proportion of patients withdrew from the study due to lack of efficacy and that the majority completed 9 months of treatment with THC/CBD spray with no increase in the number of concomitant analgesic medications suggests that this therapy is effective.

The primary efficacy measure of pain was the 0–10 NRS score that showed an improvement within the first 4 weeks of treatment, especially and not surprisingly in the patients previously exposed to placebo. This positive response was maintained with moderate continuing improvement over the 9-month treatment period being reported by more than half of the patients reaching the final visit. After 9 months of open-label THC/CBD spray treatment, the majority of patients remaining in this study reported a 30 % or more improvement in pain scores from their parent RCT baseline score. This is in line with the findings from the allodynia parent RCT, in which there was a statistically significant improvement in this outcome measure when THC/CBD spray was compared with placebo [17].

In the SGIC efficacy measure, the majority of patients reported an overall improvement in their PNP at the end of

treatment. This is in line with both parent RCTs, in which the improvements in favour of THC/CBD spray versus placebo reached statistical significance in the allodynia RCT [17], but not the diabetic neuropathy RCT [18]. Similar improvements in patient quality of life and pain intensity scores have been reported in other clinical trials of evoked pain using cannabinoids [11, 16, 23–25].

Sustained improvements from baseline were also observed in NPS and sleep quality 0–10 NRS scores. These findings suggest that efficacy is maintained with long-term THC/CBD spray treatment in the majority of patients, an encouraging finding in this normally treatment-resistant patient population. The importance of sleep in chronic pain states has been well documented [26, 27] and one of the main objectives for patients is to gain improved sleep [28], especially since neuropathic pain can be worse at night [29]. Improvements in sleep quality with THC/CBD spray have also been published in both short- and long-term clinical trials [13, 14, 16, 22] including the parent allodynia RCT to the current study, in which a statistically significant improvement in sleep quality was also observed [17]. In addition to THC/CBD spray, these improved sleep quality findings are also consistent with recent studies which looked at other cannabinoid medicines, such as smoked cannabis [24] and synthetic THC [25].

A further positive outcome was that, over the course of the study, there was no evidence of a tolerance developing towards THC/CBD spray, with the median number of daily sprays of THC/CBD spray reducing from 8.0 daily sprays after 1 month of treatment to 6.6 daily sprays during the last month of treatment. Furthermore, the incidence of AEs for this population, who had relatively severe neuropathic pain and were receiving polypharmacy, was reasonably low. The most common treatment-related AEs were dizziness and nausea. These reactions are both well characterised and easily managed and appear to have no long-term sequelae. The majority of AEs resolved and were considered to be either mild or moderate in severity. 23 % of patients discontinued THC/CBD spray due to AEs. By contrast, a meta-analysis of long-term opioid use for chronic non-cancer pain showed 34 % of patients discontinued strong oral opioids due to AEs [30]. No increase in intoxication was observed with long-term use of THC/CBD spray and no new significant safety issues were raised as a result of the study.

Two deaths were reported during this study, but neither was considered related to THC/CBD spray. Four SAEs were considered related to study treatment. These consisted of two events of amnesia, one event of paranoia and one event of suicidal attempt. All events had resolved by the end of the study with the exception of one event of amnesia. There was another event of suicidal ideation that was considered unrelated to THC/CBD spray.

The lifetime prevalence of suicidal ideation in the general population of Europe is estimated at 7.8 % [31]; in chronic pain, this prevalence has been reported to be approximately three times higher at 20 % [32]. Relative to control subjects, the risk of death by suicide was found to at least double in patients with chronic pain, with a lifetime prevalence of suicide attempts of between 5 and 14 % in individuals with chronic pain [32]. Pain and depression coexist [33, 34] as do depression and suicide [35, 36]. Therefore, it is not surprising that the prevalence of depression in chronic pain augments a higher risk of suicidal ideation and suicide attempts. During this 9-month study, the overall incidence of AEs of depressed mood and depression was reasonably low ($\leq$3 %). The relatively high incidence of suicide attempts in the general chronic pain population and the other confounding factors in these two cases, which included previous suicide attempts, depression related to diabetes/chronic pain and difficult social circumstances, suggests a direct causality with THC/CBD spray is unlikely.

Study limitations

As this was an open-label study with no possibility of comparing with a placebo, it is possible that the observed maintenance of efficacy with THC/CBD spray could be attributable to causes other than the study medication. These include changes in the underlying disease across time or changes in the set of patients in the study- and efficacy-related withdrawals. As such, a randomised withdrawal study would further ascertain whether efficacy of THC/CBD spray is maintained after long-term treatment. This was attempted as an addition to the current study, yet no clear efficacy conclusions could be reached due to low numbers of participants (19 patients), many of which were non-responders to initial THC/CDB treatment.

Conclusions

In conclusion, neuropathic pain can be a distressful and disabling condition with existing management options providing insufficient relief for patients and often causing a significant number of side effects. The patients enrolled in this study had advanced long-lasting treatment-resistant disease and were significantly disabled. The results of this study show that THC/CBD spray is an efficacious option in neuropathic pain management that can be maintained for long-term use. Furthermore, patients who continue to use THC/CBD spray for the duration of the study do not increase their daily dose, nor do they seek to increase their use of other pain-relieving medications over time. This study meets the objectives described in the CHMP

neuropathic pain guidelines [19] regarding maintenance and/or development of tolerance to the effect of the medicine. The benefits for these patients seem to outweigh the risks of treatment and suggest that THC/CBD spray may provide an effective option for patients with neuropathic pain.

Conflicts of interest B. Hoggart, S. Ratcliffe, E. Ehler, K. H. Simpson, J. Hovorka, J. Lejčko and M. Serpell were all investigators in this study and received investigator fees from GW Pharma Ltd. accordingly for their participation in the study. GW Medical Writers L. Taylor, H. Lauder and S. M. Greenwood 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 vested in or exclusively licenced to GW.

Ethical standards The study was approved by the Institutional Review Boards or Ethical Committees in each of the countries in which it was run and was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines.

Informed consent All patients gave informed consent prior to their inclusion in the study and before any study-related procedures were carried out.

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