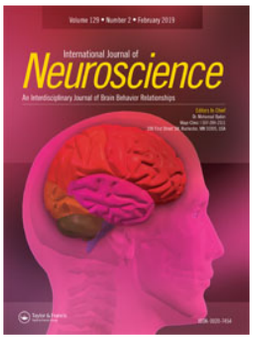

International Journal of Neuroscience

ISSN: 0020-7454 (Print) 1543-5245 (Online) Journal homepage: https://www.tandfonline.com/loi/ines20

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To cite this article: Jolana Markovà, Ute Essner, Bülent Akmaz, Marcella Marinelli, Christiane Trompke, Arnd Lentschat & Carlos Vila (2019) Sativex® as add-on therapy vs. further optimized first-line ANTispastics (SAVANT) in resistant multiple sclerosis spasticity: a double-blind, placebo-controlled randomised clinical trial, International Journal of Neuroscience, 129:2, 119-128, DOI: 10.1080/00207454.2018.1481066

To link to this article: https://doi.org/10.1080/00207454.2018.1481066

INTERNATIONAL JOURNAL OF NEUROSCIENCE
2019, VOL. 129, NO. 2, 119–128
https://doi.org/10.1080/00207454.2018.1481066

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ORIGINAL ARTICLE

Sativex® as add-on therapy vs. further optimized first-line ANTispastics (SAVANT) in resistant multiple sclerosis spasticity: a double-blind, placebo-controlled randomised clinical trial

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ABSTRACT

Purpose/aim: To evaluate the efficacy of tetrahydrocannabinol (THC):cannabidiol (CBD) oromucosal spray (Sativex®) as add-on therapy to optimised standard antispasticity treatment in patients with moderate to severe multiple sclerosis (MS) spasticity.

Methods: Sativex® as add-on therapy vs. further optimised first-line ANTispastics (SAVANT) was a two-phase trial. In Phase A, eligible patients received add-on THC:CBD spray for 4 weeks to identify initial responders [≥20% improvement from baseline in spasticity 0–10 numerical rating scale (NRS) score]. Following washout, eligible initial responders were randomised to receive THC:CBD spray or placebo for 12 weeks (double-blinded, Phase B). Optimisation of underlying antispasticity medications was permitted in both groups across all study periods.

Results: Of 191 patients who entered Phase A, 106 were randomised in Phase B to receive add-on THC:CBD spray ($n = 53$) or placebo ($n = 53$). The proportion of clinically relevant responders after 12 weeks (≥30% NRS improvement; primary efficacy endpoint) was significantly greater with THC:CBD spray than placebo (77.4 vs. 32.1%; $p < 0.0001$). Compared with placebo, THC:CBD spray also significantly improved key secondary endpoints: changes in mean spasticity NRS ($p < 0.0001$), mean pain NRS ($p = 0.0013$), and mean modified Ashworth's scale ($p = 0.0007$) scores from Phase B baseline to week 12. Adverse events, when present, were mild/moderate and without new safety concerns.

Conclusions: Add-on THC:CBD oromucosal spray provided better and clinically relevant improvement of resistant MS spasticity compared with adjusting first-line antispasticity medication alone.

ARTICLE HISTORY
Received 20 February 2018
Revised 10 May 2018
Accepted 21 May 2018

KEYWORDS
Multiple sclerosis; spasticity; Sativex®; THC:CBD; nabiximols

Introduction

Spasticity is a common chronic symptom in patients with multiple sclerosis (MS) which increases in prevalence and severity as the disease progresses [1–3]. It is frequently accompanied by pain, spasms, mobility restrictions, sleep disturbances, and/or bladder dysfunction and is strongly associated with fatigue, anxiety, and depression [4,5]. Patients' quality of life worsens as spasticity severity increases [6–8].

Interventional procedures (e.g. physiotherapy) and pharmacological therapy are the main approaches for treating MS spasticity. Baclofen and tizanidine are recommended first-line pharmacological options in the European Union (EU) [4,9], and dantrolene is indicated in certain countries (albeit used less often). However, treatment with these conventional oral antispasticity medications is often limited by undesired adverse effects, including effects on the central nervous system (CNS), increased risk of falls, and/or by a waning effect as MS progresses [10]. About one-third of MS patients continue to experience moderate to severe spasticity despite first-line treatment [11–13], and a relevant proportion of patients and physicians are dissatisfied with standard antispasticity medications [7].

Randomised clinical trials [14–16] and observational studies conducted in routine clinical practice [17,18] have shown that an oromucosal spray of tetrahydrocannabinol (THC) and cannabidiol (CBD) (Sativex®, Nabiximols USAN name) is an effective and well-tolerated option for treating resistant MS spasticity.

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THC:CBD spray is approved in several countries (e.g. Canada, Germany, Italy, Spain, and UK) and across Europe it is indicated as add-on therapy for patients with moderate to severe MS spasticity who have not responded adequately to first-line antispasticity medications [19]. This indication has raised a clinical question in terms of how much greater the benefits of THC:CBD spray might be compared with those achieved by attempting to further optimise standard first-line oral antispasticity therapy.

Herein, we report results from the Sativex® as Add-on therapy vs. further optimised first-line ANTispastics (SAVANT) randomised, placebo-controlled trial which was designed to evaluate the therapeutic efficacy of add-on THC:CBD spray compared with further optimisation of standard antispasticity therapy in patients with moderate to severe MS spasticity who were not achieving adequate symptomatic relief after use of two or more optimised first-line antispasticity medications.

Methods

Design and participants

SAVANT was a prospective, randomised, parallel group, double-blind, placebo-controlled two-phase trial. Patients were enrolled at 15 sites, 14 in the Czech Republic and 1 in Austria.

Main inclusion criteria were adults ≥18 years of age, with a diagnosis of MS and existing MS spasticity symptoms for at least 12 months; moderate to severe MS spasticity defined as a score of ≥4 on the MS spasticity 0–10 NRS scale; previous treatment with at least two different optimised oral MS spasticity therapies which included oral baclofen and/or oral tizanidine (as monotherapy or in combination therapy); currently receiving optimised treatment with one or more oral antispasticity drugs (baclofen and/or tizanidine and/or dantrolene as monotherapy or in combination therapy) for at least 3 months prior to screening without adequate relief of MS spasticity symptoms. Optimisation was defined as reporting achievement of the most effective and best tolerated dose possible according to approved labelling. Patients provided written informed consent to participate.

Exclusion criteria included prior administration of THC:CBD spray; current consumption of cannabis herb or other cannabinoid-based drugs within 30 d prior to study entry; treatment with botulinum toxin injection for spasticity relief within the previous 6 months; medical history or family history of major psychiatric disorders other than depression; known or suspected history of a dependence disorder or heavy alcohol consumption; possibility of pregnancy or lactation; history of myocardial infarction or clinically significant cardiac dysfunction; clinically significant impaired renal function or impaired hepatic function.

The study design is illustrated in Figure 1. In a single-blind, 4-week, trial period (Phase A), patients received THC:CBD spray as add-on therapy to optimised standard antispasticity medication. Patients up-

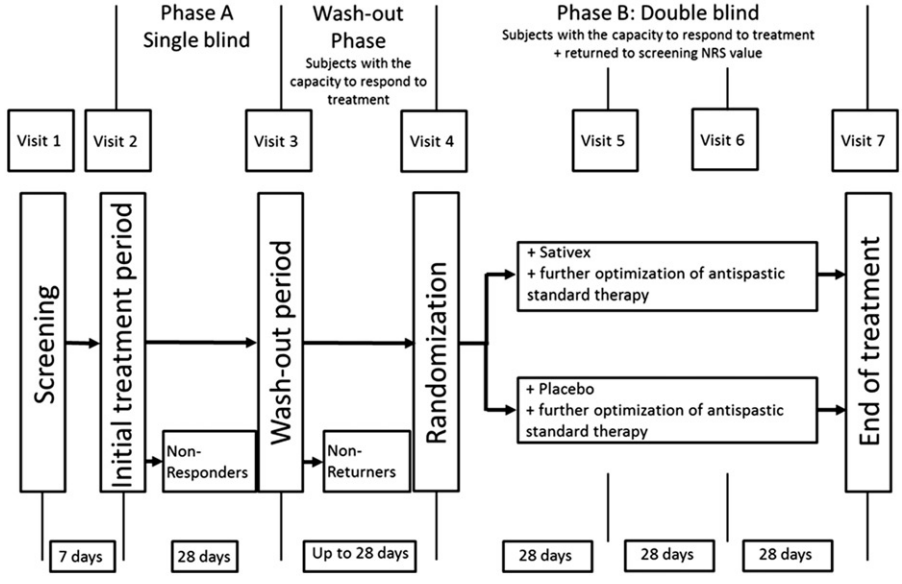

Figure 1. Overview of study design. Non-returners were initial responders who failed to show a ≥80% reduction of their Phase A NRS improvement during washout.

titrated the dosage of THC:CBD spray to a maximum of 12 sprays/day according to posology in the approved label [19] until optimised symptom relief was achieved. Initial responders were identified based on having achieved a minimal clinically important difference (MCID) in MS spasticity, defined as ≥20% improvement from baseline in the MS spasticity 0–10 NRS score, which was rounded up from the 18% improvement calculated as a MCID [20]. Non-responders were removed from the study. Initial responders at 4 weeks entered a 1- to 4-week washout phase designed to minimise carry-over effects, during which THC:CBD spray was withdrawn but underlying standard antispasticity treatment was continued. Initial responders whose improvement in the MS spasticity NRS score during Phase A was reduced by ≥80% during the washout period were eligible for Phase B. In Phase B, patients were randomised in a double-blind manner to treatment with THC:CBD spray or placebo for 12 weeks. Patients were advised to re-up-titrate their study medication to the optimal individual dose identified in Phase A, then to maintain the study treatment at this dose while allowing for adjustments according to the patient's needs. Optimisation of underlying antispasticity medications was permitted across all study periods.

The study comprised seven clinic visits: screening (Visit 1); start of single-blind THC:CBD spray trial period in Phase A (baseline visit, Visit 2); start of washout phase (Visit 3); start of randomised double-blind treatment in Phase B (Visit 4); then at 4-weekly intervals during the 12-week treatment period (Visits 5 to 7, end of treatment). Patients therefore participated in the study for a maximum total duration of 18–22 weeks (Figure 1).

The study was conducted in accordance with the recommendations set out in the Declaration of Helsinki (Seoul 2008) and in compliance with the ICH Consolidated Guideline for Good Clinical Practice and applicable local laws and regulations.

The EudraCT allocated number was 2015-004451-40.

Outcomes

The primary efficacy endpoint was the proportion of responders after 12 weeks of randomised treatment in Phase B, where responder was defined as a patient who achieved ≥30% improvement (i.e. a clinically important difference [CID]) in the MS spasticity 0–10 NRS score from Phase B baseline [20].

Secondary efficacy variables were measures of spasticity and associated symptoms during the 12-week randomised treatment period (Phase B). Changes referred to values at study end compared with values at Phase B baseline:

- Change from baseline in MS spasticity 0–10 NRS score
- Change from baseline in pain 0–10 NRS score
- Change from baseline in modified Ashworth scale (MAS) score
- Change from baseline in Expanded Disability Status Scale (EDSS) score.

Other secondary efficacy endpoints were frequency and severity of spasms; sleep disruption 0–10 NRS score; modified Ashworth scale score per muscular group; Barthel activities of daily living (ADL) index; short-form 36 quality of life (QoL) health survey (SF-36); global assessment of clinical change (GIC) by subject (SGIC) and physician (PGIC); and timed 10-metre walk test. Safety and tolerability outcomes were collected during the Phase A, washout, and Phase B periods and assessed separately. The number of patients with adverse events (AEs) and serious adverse events (SAEs); the numbers of AEs, SAEs, and treatment interruptions related to AEs; and discontinuation rates and the reasons for discontinuation were also recorded. AEs were assessed for their intensity (mild, moderate, and severe) and causal relationship with study treatment.

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA; version 19.1) and tabulated by system organ class (SOC) and preferred term (PT).

Statistical analysis

A sample size of 82 randomised (1:1 ratio) evaluable patients in Phase B was estimated to provide 90% power to detect a difference of 35% between arms in the primary endpoint. A blinded interim analysis was performed to ensure adequacy of the sample-size calculation.

Analysis of the primary endpoint was performed for the Phase B intention-to-treat (ITT) population. An analysis was performed using the Phase B per protocol (PP) population to assess the robustness of the trial. All other efficacy variables were analysed using both the ITT and PP populations. Safety outcomes were analysed for the safety population.

The Phase B primary efficacy variable was analysed using a logistic regression model, with baseline value as a covariate and treatment group as factor. Missing data were handled using Last Observation Carried Forward (LOCF) and Generalized Linear Mixed Models

(GLMM) methods for binary repeated data with GLIMMIX SAS procedure as a sensitivity analysis.

All secondary continuous efficacy variables with repeated measures were analysed by means of a mixed model for repeated measures (MMRM). The dependent variable was the change from baseline to each scheduled post-baseline visit (encompassing all available measurements for a patient) during the treatment period. The model adjusted for baseline value as covariate and treatment, visit, and treatment-by-visit interaction as fixed effect factors.

Treatment effects and treatment comparisons were estimated by least square (LS) means and differences in LS means on the treatment-by-visit interaction at the corresponding visits, along with standard errors (SE) and 95% confidence intervals (CIs), and the *p*-value corresponding to the between-treatment group difference.

Finally, secondary binary efficacy variables with repeated measures were analysed using a GLMM model for binary repeated data with GLIMMIX SAS procedure. All secondary variables or other outcomes with one post-baseline assessment were analysed using an observed cases approach.

Continuous data were summarised using descriptive statistics and categorical data are presented using frequency (*n*) and percentage (%). All statistical hypotheses were tested at the two-sided 5% significance level ($\alpha = 0.05$), and corresponding 95% CIs are reported as appropriate.

Other secondary endpoints, exploratory endpoints and safety endpoints are presented using descriptive statistics.

Statistical analyses were performed using SAS statistical analysis software Version 9.1.3 or higher (SAS Institute Inc., Cary, NC, USA).

Results

The demographic and clinical characteristics of patients entering the Phase A trial period ($n = 191$) are summarised in Table 1. The population was predominantly female (70.2%) with a mean (SD) age of 51.3 ± 10.2 years. Most patients had secondary progressive MS ($n = 92$; 48.2%) or relapsing remitting MS ($n = 78$; 40.8%). At baseline, patients had significant disability (mean EDSS score 5.9) and moderate to severe MS spasticity (mean NRS score 6.4). Patients had a long history of MS and of MS spasticity with a mean duration of 14.2 and 7.8 years, respectively.

Table 1. Demographic and clinical characteristics of patients entering the Phase A trial period ($n = 191$).

Characteristic	Value
Gender: female/male: *n* (%)	134 (70.2%)/57 (29.8%)
Age: mean (SD)	51.3 (10.2)
MS classification, *n* (%)	
Primary progressive MS	21 (11.0%)
Secondary progressive MS	92 (48.2%)
Relapsing remitting MS	78 (40.8%)
MS disease history, years: mean (SD)	14.2 (8.4)
EDSS score: mean (SD)	5.9 (1.1)
Disease modifiers use, *n* (%)	
Past	191 (100%)
Present	190 (99.5%)
MS spasticity history, years: mean (SD)	7.8 (5.3)
NRS spasticity score: mean (SD)	6.4 (1.2)
Pain NRS: mean (SD)	5.5 (1.9)

Most patients in the Phase A safety population had received baclofen (99.0%) and/or tizanidine (89.0%) as prior antispasticity medication, and 77.5% had taken a combination of baclofen and tizanidine. No patient had received dantrolene as prior antispasticity medication. Other previous antispasticity medications taken by patients included other centrally acting agents (14.6%) and benzodiazepine derivatives (8.4%). At Phase A baseline, 82.2% of patients were receiving baclofen and 34.5% were receiving tizanidine (inclusive of patients receiving combination therapy). The demographic and clinical characteristics of Phase B patients were similar to those in the Phase A population. At Phase B baseline, 84.9% of patients were receiving baclofen, 31.1% were receiving tizanidine, and 16.0% were receiving combination therapy.

Patient disposition during all phases of the study is shown in Figure 2. Following trial therapy with THC:CBD spray in Phase A, 134 patients (70.5%) were initial responders ($\geq$20% NRS improvement). Of these, 106 patients (i.e. 55.5% of 191 Phase A patients) had a $\geq$ 80% reduction of their Phase A NRS improvement during the washout period and were eligible for randomisation into Phase B. A total of 50/53 patients (94.3%) allocated to THC:CBD spray and 46/53 patients (88.8%) allocated to placebo completed 12 weeks of double-blind treatment.

Efficacy

The primary efficacy endpoint, the proportion of MS spasticity 0–10 NRS CID responders after 12 weeks of randomised treatment, was significantly higher in the THC:CBD oromucosal spray group (41/53; 77.4%) than in the placebo group (17/53; 32.1%), with an adjusted odds ratio of 7.0 (95% CI: 2.95–16.74; $p < 0.0001$; ITT population; Figure 3).

At week 4 in Phase B, 81.1% of patients allocated to THC:CBD spray had reached the initial response threshold of $\geq$20% NRS improvement versus 45.3% in the placebo group ($p = 0.0007$).

The mean (SD) number of sprays/day of THC:CBD spray was 7.7 (3.0) at week 4 of Phase A ($n = 188$) and

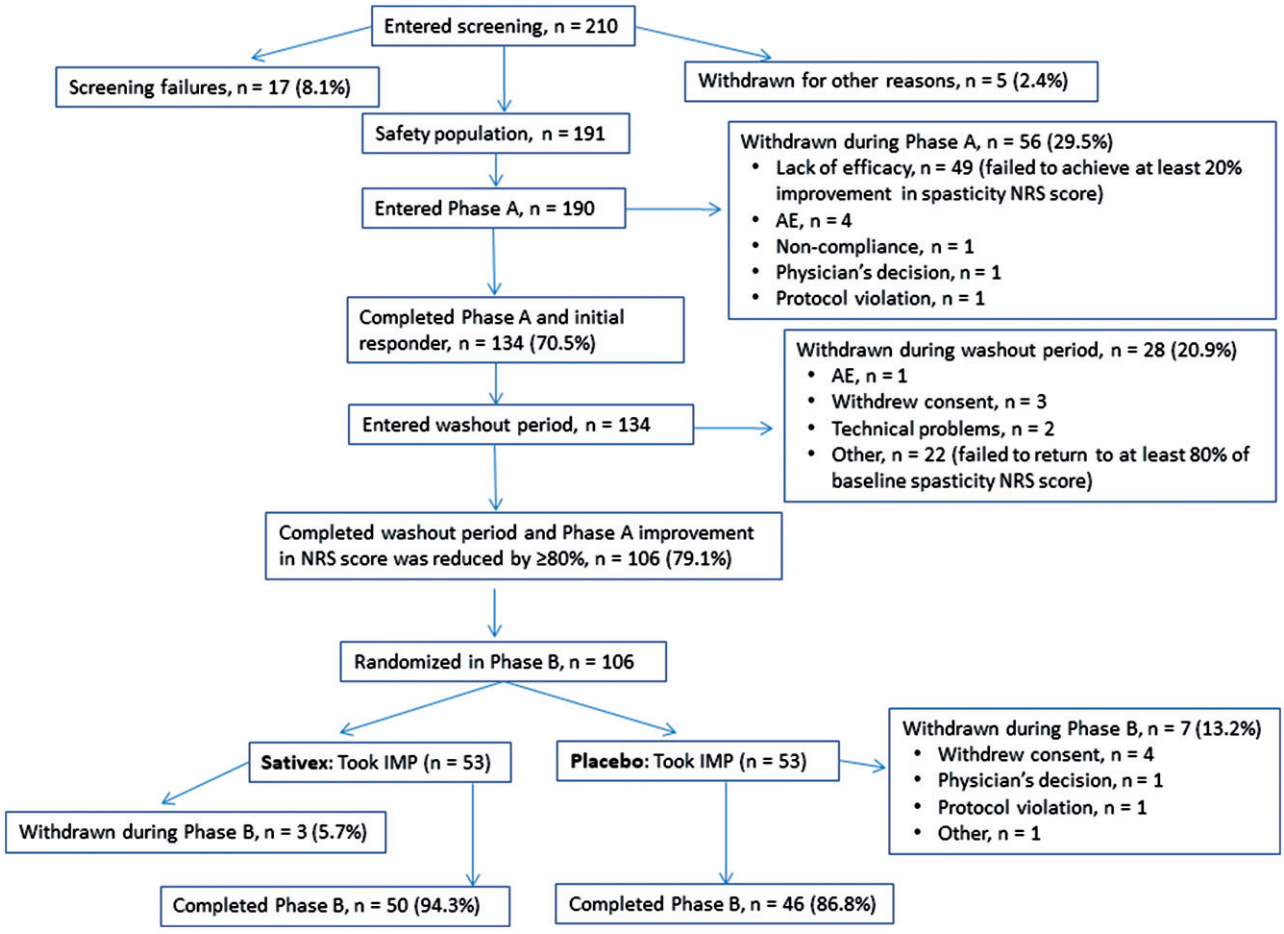

Figure 2. Patient disposition. IMP: investigational medicinal product; NRS: numerical rating scale.

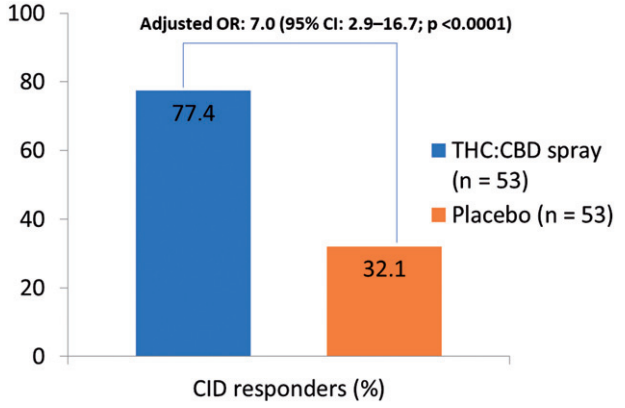

Figure 3. Primary endpoint: proportion of MS spasticity 0–10 NRS CID responders (≥30% improvement from baseline) after 12 weeks' randomised double-blind treatment with THC:CBD oromucosal spray or placebo. CI: confidence interval; CID: clinically important difference; NRS: numerical rating scale; OR: odds ratio.

7.5 (2.6) at week 4 of randomised Phase B ($n = 102$). At the week 12 final visit (study end), the mean (SD) number of sprays/day was 7.3 (2.7) for THC:CBD spray ($n = 48$) and 8.5 (3.0) for placebo ($n = 46$).

Mean (SD) doses of underlying antispasticity study medication were 35.8 (25.5) mg for baclofen and 5.2 (3.0) mg for tizanidine in Phase A and 35.4 (25.5) mg for baclofen and 5.1 (2.9) mg for tizanidine in Phase B. During Phase B, seven patients (two in the THC:CBD oromucosal spray group and five in the placebo group) re-adjusted their baclofen doses.

The results of secondary efficacy outcomes are shown in Table 2. At week 12 in Phase B, significant reductions were observed with THC:CBD spray versus placebo in the mean MS spasticity 0–10 NRS score ($p < 0.0001$; Figure 4), mean pain 0–10 NRS score ($p < 0.0013$), and mean 0–4 MAS score ($p < 0.0007$). The difference between THC:CBD spray and placebo for the change in mean MS EDSS scores from Phase B baseline to week 12 was not significant. Among other secondary efficacy assessments, THC:CBD spray was significantly superior to placebo for spasms severity ($p = 0.0001$), sleep disruption ($p = 0.0006$), and MAS scores for seven of 10 tested muscular groups (elbow flexor, extensor and pronator, hip adductor, knee flexor and extensor and foot plantar).

Table 2. Secondary efficacy endpoints: least squares (LS) means for change in measures of spasticity and associated symptoms from Phase B baseline to week 12.

Endpoint	THC:CBD oromucosal spray (mean) ($n = 53$)	Placebo (mean) ($n = 53$)	Treatment difference	*P* value
Spasticity NRS score, 0–10 scale	−3.5	−1.6	−1.9	<0.0001
Pain NRS score, 0–10 scale	−3.2	−1.8	−1.4	<0.0013
MAS score, 6-point ordinal scale	−0.30	−0.06	−0.24	<0.0007
MS EDSS score, 0–10 scale	−0.02	−0.01	−0.01	0.6529
Spasms frequency, *n*	−20.58	−17.75	−2.83	ns
Spasms severity, 0–3 scale	−0.72	−0.38	−0.34	0.0001
Sleep disruption NRS score, 0–10 scale	−3.21	−1.78	−1.43	0.0006
MAS score per muscular group, 0–4 scale				
Elbow flexor	−0.28	−0.03	−0.24	0.0044
Elbow extensor	−0.31	−0.01	−0.30	0.0004
Elbow pronator	−0.23	−0.02	−0.20	0.0327
Elbow supinator	−0.16	−0.02	−0.14	ns
Wrist flexor	−0.16	−0.04	−0.12	ns
Finger flexor	−0.16	−0.02	−0.14	ns
Hip adductor	−0.43	−0.09	−0.34	0.0007
Knee flexor	−0.47	−0.11	−0.36	0.0016
Knee extensor	−0.51	−0.13	−0.38	0.0004
Foot plantar	−0.33	−0.10	−0.22	0.0119
Barthel ADL index	0.04	0.11	−0.07	ns
SF–36 (general health)	0.31	1.90	−1.59	ns
Timed 10-m walk, seconds	−2.79	−1.08	−1.71	0.11
SGIC, adjusted odds ratio and *p*-value THC:CBD vs. placebo	Week 4: 2.852, $p = 0.0035$; Week 8: 1.823, $p = 0.1331$; Week 12: 1.384, $p = 0.3515$			
PGIC, adjusted odds ratio and *p* value THC:CBD vs. placebo	Week 4: 3.972, $p = 0.00005$; Week 8: 2.418, $p = 0.0260$; Week 12: 1.623, $p = 0.1615$			

ADL: activities of daily living; EDSS: expanded disability status scale; MAS: modified Ashworth scale; MS: multiple sclerosis; NRS: numerical rating scale; ns: not significant; PGIC: physician's global impression of change; SF-36: 36-Item short form health survey; SGIC: subject's/patient's global impression of change.

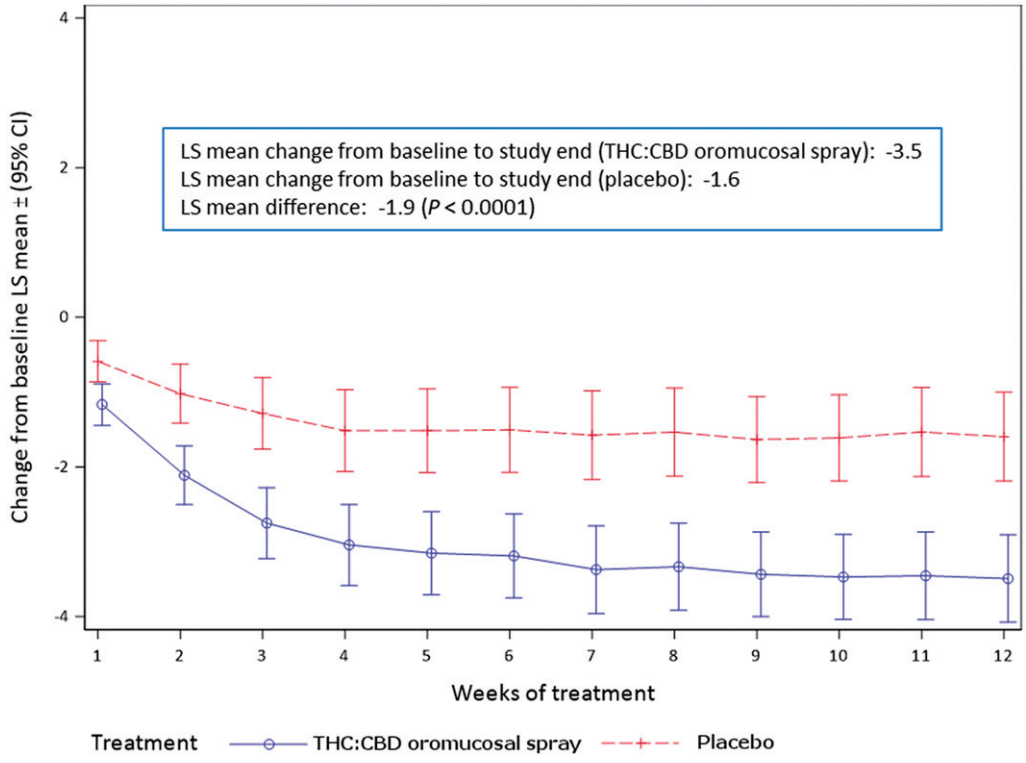

Figure 4. Change in MS spasticity 0–10 NRS score [measured in least squares (LS) means] from Phase B baseline (Week 1) through to Week 12 of randomised double-blind treatment with THC:CBD oromucosal spray ($n = 53$) or placebo ($n = 53$) in the intent-to-treat population.

Statistically significant improvements in SGIC and PGIC were reported for THC:CBD vs. placebo after 4 weeks, but tended to decrease at follow-up visits (Table 2). Most other secondary efficacy endpoints changes were in favour of THC:CBD oromucosal spray, but comparisons did not reach statistical significance.

Safety

Features of treatment emergent adverse events (TEAEs) occurring in the Phase A and washout period safety population ($n = 191$) and Phase B safety population ($n = 106$) are shown in Tables 3 and 4, respectively.

In Phase A, 75 AEs (28 moderate and 47 mild) were reported in 46 patients (24.1%), of which 64 events in 37 patients (19.4%) were considered to be related to study medication (Table 3). Three SAEs which occurred in two patients (erysipelas; olecranon bursitis and MS relapse) were considered unrelated to study treatment. There were 54 AE-related treatment interruptions in 29 patients (15.2%), and five AEs in four patients (2.1%) which led to withdrawal.

The most frequently reported TEAEs during Phase A were vertigo (15 TEAEs in 14 patients [7.3%]), somnolence (six TEAEs in three patients [1.6%]), dizziness (four TEAEs in four patients [2.1%]), diarrhoea (four TEAEs in four patients [2.1%]) and nausea (four TEAEs in four patients [2.1%]). All TEAEs except one event of vertigo were assessed as related to study treatment.

In the washout phase, 20 TEAEs in 12 patients were ongoing (i.e. carried over from Phase A or started during washout phase), of which 12 TEAEs in six patients (carried over from Phase A) were assessed as related to study medication. All TEAEs ongoing during washout were mild or moderate in intensity. The most frequently reported TEAEs were classified in the SOC *Nervous system disorders* (four TEAEs in four patients). All TEAEs were reported by single patients, except for dry mouth, dry throat and hypertension, which were reported by two patients.

During the 12-week randomised treatment phase (Phase B), no major or new safety concerns were identified for THC:CBD spray (Table 4).

There was no statistically significant difference between treatment groups in the number of patients with TEAEs (including SAEs) during Phase B: 19 TEAEs in 12 patients in the active group and 8 TEAEs in seven patients in the placebo group. All TEAEs were of either mild or moderate intensity except for one severe SAE reported in the placebo group.

There was no statistically significant difference between treatment groups in the number of patients with SAEs during Phase B: one SAE (haematuria of moderate severity) in one patient in the active group and one SAE (tubulointerstitial nephritis of severe intensity) in one patient in the placebo group, both of which began and ended in Phase B and were assessed as not related to study medication.

There was no statistically significant difference between treatment groups in the number of patients with TEAEs related to study medication during Phase B: seven TEAEs in five patients in the active group and one TEAE in one patient in the placebo group. All related TEAEs in the active group were of mild intensity, except for one event of vertigo which was of

Table 3. Treatment-emergent adverse events (TEAEs) in the Phase A and washout periods. Safety population.

			Total ($n = 191$)	
			n (%)	Events
Phase A	Serious adverse events (SAEs)		2 (1.0%)	3
	Adverse events (AEs)		46 (24.1%)	75
	Relationship to IMP	Not related to IMP	9 (4.7%)	11
		Related to IMP	37 (19.4%)	64
	Intensity	Mild	34 (17.8%)	47
		Moderate	13 (6.8%)	28
	Number of treatment interruptions[a] related to AEs		29 (15.2%)	54
	Adverse events leading to withdrawal		4 (2.1%)	5
	Adverse events leading to death		0	0
Washout	SAEs		0	0
	AEs		12 (6.3%)	20
	Relationship to IMP	Not related	6 (3.1%)	8
		Related	6 (3.1%)	12
	Intensity	Mild	6 (3.1%)	10
		Moderate	6 (3.1%)	10
	Number of treatment interruptions[a] related to AEs		6 (3.1%)	12
	Adverse events leading to withdrawal		1 (0.5%)	1
	Adverse events leading to death		0	0

IMP: investigational medicinal product.
[a]Treatment interruptions includes the following action taken with study treatment: drug withdrawn, dose reduced, or dose increased.
An adverse event that has a start and stop date in different study phases has been presented in all phases that the event was ongoing.

Table 4. Treatment-emergent adverse events (TEAEs) during the 12-week double-blind treatment period (Phase B), in the Phase B safety population.

	THC:CBD oromucosal spray ($n = 53$)		Placebo ($n = 53$)	
	n (%)	Events	*n* (%)	Events
Serious adverse events (SAEs)	1 (1.9%)	1	1 (1.9%)	1
Adverse events (AEs) including SAEs	12 (22.6%)	19	7 (13.2%)	8
Relationship to IMP				
Not related to IMP	8 (15.1%)	12	6 (11.3%)	7
Related to IMP	5 (9.4%)	7	1 (1.9%)	1
Intensity				
Moderate	6 (11.3%)	6	0	0
Mild	7 (13.2%)	13	6 (11.3%)	7
Severe	0	0	1 (1.9%)	1
Number of treatment interruptions related to AEs[a]	2 (3.8%)	3	0	0

IMP: Investigational medicinal product.
[a]Treatment interruptions includes the following action taken with study treatment: drug withdrawn, dose reduced, or dose increased.
An adverse event that has a start and stop date in different study phases has been presented in all phases that the event was ongoing.

moderate intensity. Of TEAEs deemed related to THC:CBD spray, five TEAEs in three patients were classified in SOC *Nervous system disorders* (PT: somnolence, hypoaesthesia, hypogeusia and psychomotor skills impaired). There were three treatment interruptions related to AEs in two patients (3.8%) in the active group and none in the placebo group.

Discussion

In patients with moderate-to-severe resistant MS spasticity who initially responded to THC:CBD spray during a 4-week trial period, adding THC:CBD spray to already-optimised antispasticity treatment is a better alternative to readjusting first-line antispasticity medication alone. After 12 weeks' treatment, a significantly greater proportion of patients treated with add-on THC:CBD spray than placebo achieved clinically relevant improvement ($\geq$ 30% NRS improvement) in MS spasticity, with the difference representing a +45.3% therapeutic gain in favour of THC:CBD oromucosal spray. Compared with placebo, THC:CBD spray also produced significantly greater reductions in key secondary efficacy measures including MS spasticity 0–10 NRS, pain 0–10 NRS, and MAS scores. Other secondary efficacy measures significantly in favour of THC:CBD spray included spasms severity, sleep disruption, and MAS for seven of 10 tested muscular groups. Although improvement was observed in the physical activity subscale of the SF-36 in the group treated with THC:CBD spray, overall QoL scores did not differ significantly between treatment groups, probably due to underlying MS and the presence of other MS-related symptoms (e.g. fatigue).

In accordance with standard procedures for pre-approval regulatory studies in which changes in factors other than target medication must be kept to a minimum, no alterations to underlying antispasticity medications were permitted in previous clinical development trials of THC:CBD spray [15,16,21]. However, daily clinical experience with THC:CBD spray indicates that patients can adapt their underlying antispasticity medications according to individual needs and, indeed, continuous optimisation is viewed as an integral component of gaining maximum benefit from a given treatment. The current study therefore set out to evaluate the efficacy of add-on THC:CBD spray under conditions closer to daily clinical practice by explicitly allowing optimisation of patients' underlying antispasticity therapy throughout all phases of the study and also ensuring that all participants had tried and failed at least two first-line antispasticity drugs.

The demographic and clinical characteristics of the patient population were comparable to those in previous clinical trials and observational studies of THC:CBD spray in resistant MS spasticity [16–18], allowing meaningful comparisons to be made between the studies.

At the end of the 4-week trial period of THC:CBD spray, 70.5% of patients (134/190) were initial responders ($\geq$ 20% NRS improvement). This was higher than the initial response rate of 47% (272/572 patients) reported in the enriched-design phase 3 clinical trial of THC:CBD spray [16] but identical to the initial response rate of 70.5% reported in the Italian health authorities prospective e-registry study of THC:CBD spray ($n = 1615$) [18]. The washout period eliminated 28 initial responders (20.9%) who failed to show $\geq$80% reduction in their Phase A NRS improvement. The inclusion of a washout period, and requirement for patients' spasticity levels to return to near pre-treatment levels, is the main point of difference between our study and that of Novotna et al. [16] and ensured that treatment effects observed in Phase B

were not confounded by any 'carryover' or other effects of THC:CBD spray from Phase A.

After 12 weeks of randomised treatment in initial responders, the CID responder rate was significantly in favour of THC:CBD spray over placebo (77.4 vs. 32.1%; $p < 0.0001$), demonstrating a broad therapeutic gain despite having allowed for dosage adjustments of underlying antispasticity medication in both groups. This result compares favourably with respective values of 74% and 51% (OR: 2.73; 95% CI: 1.59–4.69; $p = 0.0003$) reported in the pivotal trial of Novotna et al. [16] where the absence of a washout period between Phases A and B may have contributed to a more pronounced placebo effect [16].

Among study participants who were initial responders to THC:CBD spray in Phase A and met eligibility criteria after washout for randomisation in Phase B, 77.4% of those allocated to THC:CBD spray in Phase B achieved the CID threshold of $\geq$30% NRS improvement [20]. Thus, the probability of becoming a CID responder to THC:CBD spray upon starting treatment (start of trial period) was 43%, which is similar to the 36% reported in the phase 3 trial [16] and to the 41% reported in the Mobility ImproVEment (MOVE) 2 observational study in Germany [17].

Secondary effectiveness measures in favour of THC:CBD spray, specifically changes from Phase B baseline to study end in MS spasticity 0–10 NRS, pain 0–10 NRS, and MAS scores, further support the difference observed between THC:CBD spray and placebo in the responder rate at 12 weeks (primary endpoint) and are consistent with or superior to results reported for these endpoints in the previous enriched design trial and observational studies of THC:CBD spray conducted under approved conditions [16,17]. Although no changes were observed with THC:CBD spray or placebo on the MS EDSS, this is not surprising given that the EDSS is linked to underlying overall MS evolution, is largely ambulation driven, and has been shown to have low sensitivity to alterations in MS spasticity severity [22]. Other efficacy secondary endpoints showed trends in favour of THC:CBD spray but without reaching statistical significance. This might relate to the study power (the sample size was calculated for the primary endpoint) and also to the parameters *per se* and to the nature of MS spasticity as being one of many symptoms of MS [3].

Mean daily use of THC:CBD spray was 7.7 sprays/day at the end of Phase A and 7.3 sprays/day (versus 8.5 sprays/day for placebo) at the end of 12 weeks' treatment in Phase B. This level of usage is lower than that reported in the largest pivotal phase 3 clinical trial of THC:CBD spray (8.3 sprays/day) [16], and consistent with that reported in observational studies in daily practice (6.7–6.8 sprays/day) [17,18]. Evidence is accumulating to suggest that patients receiving THC:CBD spray in daily practice gain sufficient benefit at a mean dosage of about 7 sprays/day.

THC:CBD spray was well tolerated during both the trial and treatment phases of the study. In line with observational studies of THC:CBD spray [17,18], incidences of treatment-related AEs were low overall and any AEs reported were mainly mild or moderate in intensity and not different from those reported in the previous studies (e.g. dizziness and somnolence). The incidence of AEs related to THC:CBD spray decreased from 19.4% of patients in Phase A to 9.4% of patients in Phase B, likely reflecting accustomisation by patients during continued use, which was further supported by a decrease in the incidence of treatment interruptions related to AEs in THC:CBD spray-treated patients, from 15.2% of patients in Phase A to 3.8% of patients in Phase B.

The design of this study, especially the inclusion of a washout period to avoid carryover and other effects of THC:CBD spray during the randomised treatment phase, allowed us to better evaluate its true therapeutic effect. Under these conditions, THC:CBD spray at an average dose of about 7 sprays/day produced clinically meaningful improvement of resistant MS spasticity in more than three-quarters of initial responders, thus proving to be a more efficacious alternative to readjusting underlying antispasticity drugs.

Acknowledgements

The authors wish to express their sincere thanks for the collaboration of participating patients and investigators [CZ: Y. Benešová (Brno), M. Dufek (Brno), P. Hradílek (Havířov), L. Janů (Plzeň), H. Lachmann (Prague), B. Luběnová (Olomouc), E. Meluzínová (Prague), I. Nováková (Prague), O. Škoda (Pelhřimov), I. Štětkářová (Prague), R. Taláb (Hradec Králové), M. Vachová (Teplice), M. Vališ (Choceň); AT: M. Guger (Linz)], all team members at study sites, Easthorn CRO, and Almirall S.A. Writing assistance was provided by Content Ed Net (Madrid, Spain), with funding from Almirall S.A. (Barcelona, Spain).

Disclosure statement

J. Markovà has received fees as consultant or investigator in projects sponsored by Almirall, Amgen, Biogen, Merck, Novartis, Pfizer, Teva and other pharmaceutical companies. U. Essner and A. Lenschat are consultants for Almirall Hermal GmbH. B. Akmaz and C. Trompke are fulltime employees of Almirall Hermal GmbH. M. Marinelli and C. Vila are fulltime employees of Almirall S.A.

Funding

This study was sponsored by Almirall Hermal GmbH and Almirall S.A.

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