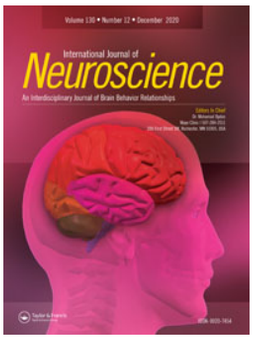

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ORIGINAL ARTICLE

Tetrahydrocannabinol and cannabidiol oromucosal spray in resistant multiple sclerosis spasticity: consistency of response across subgroups from the SAVANT randomized clinical trial

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ABSTRACT

Objective: To determine whether differences in disability status, spasticity severity, and spasticity duration at treatment start in patients with resistant multiple sclerosis (MS) spasticity might influence response to add-on tetrahydrocannabinol:cannabidiol (THC:CBD) oromucosal spray (nabiximols) versus further re-adjustment of optimized first-line antispasticity medication.

Methods: Using the database from the Sativex® as Add-on therapy Vs. further optimized first-line ANTispastics (SAVANT) study, this post hoc analysis evaluated spasticity severity (0-10 numerical rating scale [NRS] scores) and pain severity (0–10 NRS scores) evolution from randomization (baseline) to week 12 (end of double-blind treatment) in defined subgroups: Expanded disability status scale [EDSS] score subgroups (<6 and ≥ 6); spasticity severity 0-10 NRS score subgroups (4 to ≤ 6 and >6), and spasticity duration subgroups (<5 and ≥ 5 years).

Results: THC:CBD oromucosal spray (nabiximols) halved mean severity scores for spasticity and pain in all subgroups. Active treatment significantly improved mean spasticity severity scores versus placebo from week 4 onwards in both EDSS subgroups, in the severe spasticity subgroup, and in both spasticity duration subgroups. Active treatment significantly improved mean pain severity scores versus placebo in the ≥ 6 EDSS subgroup, in the severe spasticity subgroup and in both spasticity duration subgroups.

Conclusion: Add-on THC:CBD oromucosal spray (nabiximols) consistently relieves resistant spasticity across subgroups defined by baseline EDSS score, spasticity severity NRS score and spasticity duration. Patients with moderate resistant MS spasticity benefit numerically from treatment; patients with severe resistant spasticity achieve significant therapeutic gains. Spasticity-associated pain often improves similarly in the same subgroups.

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THC:CBD oromucosal spray; nabiximols; multiple sclerosis; spasticity; treatment resistance; treatment optimization

1. Introduction

Spasticity is a common and disabling symptom of multiple sclerosis (MS) [1]. Within 10 years of initial MS diagnosis, about one-third of patients are affected by moderate spasticity, and the proportion of affected patients increases over time [2]. Spasticity-associated symptoms include muscle stiffness, spasms, pain, and sleep disturbances [3]. A clear association exists between MS spasticity severity and patients' well-being and quality of life [4,5].

Currently, the main treatment modalities for generalized MS spasticity are non-pharmacological interventions (especially physiotherapy and exercise) and symptomatic oral medications [6,7]. Common first-line oral medications are baclofen and tizanidine, either as monotherapy or as combination therapy [6,7]. Due to the potential risk of dose-related side effects and individual variation in response, the usual approach with oral antispasticity medications is to initiate treatment with a single agent at a low dose and gradually titrate upwards to the maximally tolerated dose. If symptomatic relief is insufficient, it is recommended to switch to another agent. If there is still no improvement, two or more medications can be used in combination [6].

Sativex® (USAN: nabiximols), an oromucosal spray of cannabis extract containing tetrahydrocannabinol and cannabidiol (THC:CBD), is indicated in the EU and other world regions as add-on treatment for adult patients with moderate to severe resistant MS spasticity who demonstrate clinically significant improvement in spasticity-related symptoms during an initial trial of therapy [8]. Approval of THC:CBD spray (nabiximols) was granted

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based on a series of randomized controlled clinical trials demonstrating significant therapeutic efficacy versus placebo for improvement of spasticity-related symptoms [9–11]. A subsequent enriched-design study, which identified patients with an initial capacity to respond within a 4-week trial period, demonstrated significant superiority of THC:CBD spray (nabiximols) over placebo in improving patient-rated spasticity severity, spasm frequency and sleep disruption [12]. More recently, the Sativex® as Add-on therapy Vs. further optimized first-line ANTispastics (SAVANT) study showed that adding THC:CBD oromucosal spray (nabiximols) to an underlying optimized antispasticity regimen (with further dose and regimen adjustment as necessary) was more effective than re-adjusting the antispasticity medication regimen only. The SAVANT study, which followed the EU approved label for use of THC:CBD oromucosal spray (nabiximols) [8], was performed in patients with moderate to severe resistant MS spasticity receiving classical oral antispasticity medications who showed an initial response to add-on treatment with THC:CBD oromucosal spray (nabiximols) during a 4-week trial period [13].

An important clinical question in terms of further refining the use of THC:CBD oromucosal spray (nabiximols) in clinical practice is whether the therapeutic response is consistent across specific patient groups. To address this question we performed post hoc subgroup analyses of the SAVANT study data to determine whether patients' disability status, spasticity severity and spasticity duration at baseline might influence response to treatment.

2. Methods and materials

Methods applied in the SAVANT study were reported previously [13]. Briefly, SAVANT was a prospective, randomized, parallel-group, double-blind, placebo-controlled trial of THC:CBD oromucosal spray (nabiximols) as add-on therapy to optimized standard antispasticity medication in adults with moderate to severe MS spasticity. The initial study phase, consisting of a 4-week single-blind treatment period with THC:CBD oromucosal spray (nabiximols), aimed to identify initial responders (defined as patients achieving $\geq$20% improvement from baseline on the 0-10 spasticity Numerical Rating Scale [NRS]) as per the approved label [8]. Initial responders entered a 1–4 week washout phase intended to minimize the carry-over effects of active treatment. Only early responders with $\geq$80% reduction in their initial NRS improvement during washout were eligible for randomization to active treatment or placebo in the 12-week double-blind treatment phase. Study assessments were conducted at screening, start of initial treatment period, start of washout phase, randomization to double-blind treatment; and at scheduled control visits at weeks 4, 8, and 12 of double-blind treatment.

There were no additional inclusion or exclusion criteria for this post hoc analysis beyond those for the original SAVANT study [13].

The data source for this post hoc efficacy analysis of THC:CBD oromucosal spray (nabiximols) in predefined patient subgroups was the original (locked during blinding) database of the SAVANT study which had already identified patients with an initial response to active treatment.

For post hoc analyses of evolution in mean spasticity 0-10 NRS scores and mean pain 0-10 NRS scores during double-blind treatment, patient subgroups were stratified according to the following criteria:

1. Expanded Disability Status Scale (EDSS) scores at randomization: $<$6 (ambulatory) or $\geq$6.
2. Spasticity 0-10 NRS scores at randomization: 4 to $\leq$6 (moderate spasticity) or $>$6 (severe spasticity).
3. MS spasticity duration at randomization: $\leq$5 or $>$5 years.

2.1. Statistical analyses

Statistical analyses were performed in the intent-to-treat (ITT) population.

Spasticity 0-10 NRS scores and pain 0-10 NRS scores at randomization and at weeks 4, 8, and 12 of double-blind treatment are reported descriptively as mean and standard deviation (SD).

Absolute scores for mean spasticity 0-10 NRS and mean pain 0-10 NRS at each study timepoint were analysed using a mixed model for repeated measures: with the change in mean spasticity scores and mean pain scores between randomization and each scheduled treatment visit as the dependent variable; with the randomization value as a covariate; and with treatment, visit, and treatment-by-visit interaction as fixed-effect factors.

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

3. Results

Of 191 patients who entered the single-blind initial treatment trial phase, 134 patients (70.2%) were

identified as initial responders and entered the washout phase. After washout, 106 patients (55.5%) fulfilled the protocol conditions and were randomized to receive THC:CBD oromucosal spray (nabiximols) ($n = 53$) or placebo ($n = 53$) in the 12-week double-blind treatment phase. Main demographic and clinical characteristics of patients at study baseline (prior to the initial treatment phase) are presented in Table 1. The population was predominantly female (70.2%) and mean (SD) age was 51.3 (10.2) years. Most patients had secondary progressive MS (48.2%) or relapsing remitting MS (40.8%); primary progressive MS was reported in 11% of cases. Mean (SD) duration of MS was 14.2 (8.4) years and mean (SD) duration of MS spasticity was 7.8 (5.3) years. At baseline, the study population had moderate to high disability (mean [SD] EDSS score of 5.9 [1.1]), moderate to severe MS spasticity (mean [SD] 0-10 NRS score of 6.4 [1.2]), and moderate pain (mean [SD] 0-10 NRS score of 5.5 [1.9]).

At baseline of the 4-week initial trial period, 82.2% of patients were receiving baclofen and 34.5% were receiving tizanidine, inclusive of patients receiving combination therapy. Demographic and clinical characteristics of randomized patients were similar to those of the trial period population. At baseline of the 12-week double-blind treatment phase, 84.9% of patients were receiving baclofen, 31.1% were receiving tizanidine, and 16.0% were receiving combination therapy.

Treatment was completed by 94.3% (50/53) of randomized patients in the THC:CBD oromucosal spray (nabiximols) group and by 88.8% (46/53) of randomized patients in the placebo group. Withdrawal of consent ($n = 4$) was the main reason for treatment discontinuation during the double-blind phase.

3.1. Post hoc analyses of mean spasticity (0-10 NRS) score evolution

Results of the post hoc analyses of mean spasticity 0-10 NRS score evolution in the ITT population stratified by EDSS scores, spasticity severity, and MS spasticity duration at randomization are presented in Tables 2–4, respectively.

Mean spasticity (0-10 NRS) scores were reduced significantly with THC:CBD oromucosal spray (nabiximols) compared with placebo irrespective of patients' disability status at randomization. In the EDSS score <6 subgroup, mean (SD) changes in spasticity scores between randomization and week 12 of treatment were –3.21 (2.34) with THC:CBD spray (nabiximols) and –1.80 (2.43) with placebo ($p = 0.0127$). Relative mean (%) changes in spasticity NRS scores were –47.34% and –27.35%, respectively. Corresponding values in the EDSS score ≥ 6 subgroup were –3.54 (1.82) with THC:CBD spray (nabiximols) and –1.43 (2.32), with placebo ($p = 0.0002$). Relative mean (%) changes in spasticity NRS scores were –50.64% and –19.83%, respectively. In each EDSS subgroup, differences between THC:CBD spray (nabiximols) and placebo were significant also at weeks 4 and 8 (Table 2).

Table 1. Demographic and clinical characteristics of patients at baseline ($n = 191$).

Characteristic	Value
Gender: female/male: *n* (%)	134 (70.2%)/57 (29.8%)
Age: mean (SD)	51.3 (10.2)
Median (range)	53.0 (27–74)
MS classification: *n* (%)	
Relapsing remitting MS	78 (40.8%)
Secondary progressive MS	92 (48.2%)
Primary progressive MS	21 (11.0%)
MS disease duration history, years: mean (SD)	14.2 (8.4)
Median (range)	13.00 (1.0–39.0)
MS spasticity duration, years: mean (SD)	7.8 (5.3)
Median (range)	7.00 (1.0–30.0)
0–10 EDSS score: mean (SD)	5.9 (1.1)
Median (range)	6.00 (2.5–8.5)
0–10 Spasticity NRS score: mean (SD)	6.4 (1.2)
Median (range)	6.57 (3.3–9.9)
0–10 Pain NRS score: mean (SD)	5.5 (1.9)
Median (range)	5.71 (0.0–9.9)

EDSS: expanded disability status scale; MS: multiple sclerosis; NRS: numerical rating scale; SD: standard deviation.

Mean spasticity (0-10 NRS) scores were reduced with THC:CBD oromucosal spray (nabiximols) compared with placebo for patient subgroups with 0-10 NRS scores of ≤ 6 (moderate spasticity) or >6 (severe spasticity) at randomization. Differences reached the statistical significance threshold in the spasticity severity >6 subgroup. In the spasticity severity ≤ 6 subgroup, mean (SD) changes in spasticity (0-10 NRS) scores between randomization and week 12 of treatment were –2.70 (1.65) with THC:CBD spray (nabiximols) and –1.66 (1.72) with placebo ($p = 0.1373$). Relative mean (%) changes in spasticity NRS scores were –50.66% and –31.50%, respectively. Corresponding values in the spasticity severity > 6 subgroup were –3.68 (2.16) with THC:CBD spray (nabiximols) and –1.60 (2.59), with placebo ($p < 0.0001$). Relative mean (%) changes in spasticity NRS scores were –49.0% and –21.11%, respectively. In the spasticity severity >6 subgroup, differences between THC:CBD spray (nabiximols) and placebo were significant also at weeks 4 and 8 (Table 3).

Mean spasticity (0-10 NRS) scores were reduced significantly with THC:CBD oromucosal spray (nabiximols) compared with placebo irrespective of MS spasticity duration. In the patient subgroup with spasticity

Table 2. Mean spasticity 0-10 NRS score evolution in the ITT population stratified by EDSS score at randomization.

	EDSS score < 6					EDSS score ≥ 6				
	THC:CBD oromucosal spray		Placebo			THC:CBD oromucosal spray		Placebo		
Visit	*n*	Mean (SD) spasticity NRS score	*n*	Mean (SD) spasticity NRS score	*p*	*n*	Mean (SD) spasticity NRS score	*n*	Mean (SD) spasticity NRS score	*p*
Baseline	24	6.78 (1.45)	24	6.58 (1.35)	–	29	6.99 (1.22)	29	7.21 (1.27)	–
Week 4	24	3.94 (2.13)	24	5.19 (2.21)	0.0161	29	3.79 (1.82)	28	5.70 (2.19)	0.0029
Week 8	23	3.54 (2.22)	23	4.83 (2.51)	0.0181	28	3.64 (1.95)	24	5.93 (2.38)	0.0004
Week 12	22	3.48 (2.31)	23	4.78 (2.60)	0.0127	26	3.47 (1.85)	23	5.86 (2.35)	0.0002
Δ vs. baseline		−3.21 (2.34) (−47.34%)		−1.80 (2.43) (−27.35%)			−3.54 (1.82) (−50.64%)		−1.43 (2.32) (−19.83%)	

EDSS: expanded disability status scale; ITT: intent-to treat; NRS: numerical rating scale; SD: standard deviation.

Table 3. Mean spasticity 0-10 NRS score evolution in the ITT population stratified by spasticity severity at randomization.

	Spasticity NRS score ≤ 6					Spasticity NRS score > 6				
	THC:CBD oromucosal spray		Placebo			THC:CBD oromucosal spray		Placebo		
Visit	n	Mean (SD) spasticity NRS score	*n*	Mean (SD) spasticity NRS score	*p*	*n*	Mean (SD) spasticity NRS score	*n*	Mean (SD) spasticity NRS score	*p*
Baseline	15	5.33 (0.65)	15	5.27 (0.78)	–	38	7.51 (0.95)	38	7.58 (0.84)	–
Week 4	15	2.96 (1.51)	14	3.97 (1.63)	0.2014	38	4.21 (2.01)	38	6.02 (2.13)	0.0002
Week 8	14	2.77 (1.30)	14	3.64 (1.82)	0.274	37	3.91 (2.21)	33	6.13 (2.37)	<0.0001
Week 12	14	2.61 (1.30)	13	3.62 (1.98)	0.1373	34	3.83 (2.21)	33	5.99 (2.40)	<0.0001
Δ vs Baseline		−2.70 (1.65) (−50.66%)		−1.66 (1.72) (−31.50%)			−3.68 (2.16) (−49.0%)		−1.60 (2.59) (−21.11%)	

ITT: intent-to treat; NRS: numerical rating scale; SD: standard deviation.

Table 4. Mean spasticity 0-10 NRS score evolution in the ITT population stratified by MS spasticity duration.

	MS spasticity ≤ 5 years					MS spasticity > 5 years				
	THC:CBD oromucosal spray		Placebo			THC:CBD oromucosal spray		Placebo		
Visit	n	Mean (SD) spasticity NRS score	n	Mean (SD) spasticity NRS score	*p*	n	Mean (SD) spasticity NRS score	n	Mean (SD) spasticity NRS score	*p*
Baseline	23	6.94 (1.27)	21	6.98 (1.38)	–	30	6.86 (1.38)	32	6.89 (1.31)	–
Week 4	23	4.32 (1.96)	21	5.72 (2.33)	0.0245	30	3.50 (1.90)	31	5.29 (2.12)	0.0013
Week 8	21	4.04 (2.04)	20	5.50 (2.69)	0.0192	30	3.28 (2.04)	27	5.31 (2.37)	0.0004
Week 12	18	4.03 (2.26)	20	5.55 (2.67)	0.0073	30	3.15 (1.87)	26	5.14 (2.41)	0.0004
Δ vs. baseline		−3.71 (2.14) (−54.08%)		−1.73 (2.32) (−25.11%)			−2.86 (1.85) (−41.21%)		−1.47 (2.46) (−21.06%)	

ITT: intent-to treat; MS: multiple sclerosis; NRS: numerical rating scale; SD: standard deviation.

duration ≤5 years, mean (SD) changes in spasticity (0-10 NRS) scores between randomization and week 12 of treatment were −3.71 (2.14) and −1.73 (2.32), respectively ($p = 0.0073$). Relative mean (%) changes in spasticity NRS scores were −54.08% and −25.11% respectively. Corresponding values in the subgroup with spasticity duration >5 years were −2.86 (1.85) with THC:CBD spray (nabiximols) and −1.47 (2.46) with placebo ($p = 0.0004$). Relative mean (%) changes in spasticity NRS scores were −41.21% and −21.06%, respectively. In each spasticity duration subgroup, differences between THC:CBD spray (nabiximols) and placebo were significant also at weeks 4 and 8 (Table 4).

3.2. Post hoc analyses of mean pain (0-10 NRS) score evolution

Results of post hoc analyses of mean pain (0-10 NRS) score evolution stratified by EDSS scores, spasticity severity, and spasticity duration at randomization are presented in Tables 5–7, respectively.

Mean pain NRS scores were reduced with THC:CBD oromucosal spray (nabiximols) compared with placebo in patients with EDSS scores of <6 or ≥6 at randomization, with statistically significant differences in the EDSS score ≥6 subgroup. In the EDSS score <6 subgroup, mean (SD) changes in pain NRS scores between randomization and week 12 of treatment were −2.50

Table 5. Mean pain 0-10 NRS score evolution in the ITT population stratified by EDSS score at randomization.

	EDSS score < 6					EDSS score ≥ 6				
	THC:CBD oromucosal spray		Placebo			THC:CBD oromucosal spray		Placebo		
Visit	*n*	Mean (SD) pain NRS score	*n*	Mean (SD) pain NRS score	*p*	*n*	Mean (SD) pain NRS score	*n*	Mean (SD) pain NRS score	*p*
Baseline	24	5.58 (2.75)	24	5.97 (1.92)	–	29	6.43 (1.76)	29	6.26 (2.47)	–
Week 4	24	3.24 (2.21)	24	4.49 (2.33)	0.1018	29	3.18 (1.83)	28	4.57 (2.52)	0.0062
Week 8	23	2.84 (2.37)	23	4.21 (2.62)	0.1044	28	3.14 (1.70)	24	4.66 (2.91)	0.0017
Week 12	22	2.85 (2.46)	23	4.14 (2.62)	0.1284	26	2.86 (1.99)	23	4.56 (2.75)	0.003
Δ vs Baseline		−2.50 (2.37) (−44.80%)		−1.85 (2.29) (−30.99%)			−3.49 (2.41) (−54.82%)		−1.98 (2.02) (−31.63%)	

EDSS: expanded disability status scale; ITT: intent-to treat; NRS: numerical rating scale; SD: standard deviation.

Table 6. Mean pain 0-10 NRS score evolution in the ITT population stratified by spasticity severity at randomization.

	Spasticity NRS score ≤ 6					Spasticity NRS score > 6				
	THC:CBD oromucosal spray		Placebo			THC:CBD oromucosal spray		Placebo		
Visit	*n*	Mean (SD) pain NRS score	*n*	Mean (SD) pain NRS score	*p*	*n*	Mean (SD) pain NRS score	*n*	Mean (SD) pain NRS score	*p*
Baseline	15	4.58 (1.91)	15	4.49 (1.10)	–	38	6.62 (2.17)	38	6.78 (2.22)	–
Week 4	15	2.33 (1.11)	14	3.05 (1.35)	0.3242	38	3.56 (2.16)	38	5.08 (2.50)	0.0022
Week 8	14	2.26 (1.29)	14	2.62 (1.45)	0.5952	37	3.29 (2.17)	33	5.21 (2.82)	0.0002
Week 12	14	2.10 (1.47)	13	2.73 (1.57)	0.4979	34	3.17 (2.38)	33	4.99 (2.75)	0.0008
Δ vs. Baseline		−2.36 (1.51) (−51.53%)		−2.07 (1.54) (−46.10%)			−3.31 (2.67) (−50.0%)		−1.85 (2.35) (−27.29%)	

ITT: intent-to treat; NRS: numerical rating scale; SD: standard deviation.

Table 7. Mean pain 0-10 NRS score evolution in the ITT population stratified by MS spasticity duration at randomization.

	MS spasticity ≤ 5 years					MS spasticity > 5 years				
	THC:CBD oromucosal spray		Placebo			THC:CBD oromucosal spray		Placebo		
Visit	*n*	Mean (SD) pain NRS score	*n*	Mean (SD) pain NRS score	*p*	*n*	Mean (SD) pain NRS score	*n*	Mean (SD) pain NRS score	*p*
Baseline	23	6.29 (2.25)	21	6.57 (2.09)	–	30	5.86 (2.32)	32	5.84 (2.29)	–
Week 4	23	3.75 (2.13)	21	5.32 (2.68)	0.0214	30	2.79 (1.80)	31	3.99 (2.09)	0.0207
Week 8	21	3.75 (2.20)	20	5.07 (3.09)	0.0401	30	2.48 (1.72)	27	3.97 (2.42)	0.0039
Week 12	18	3.66 (2.58)	20	5.05 (2.83)	0.0307	30	2.37 (1.80)	26	3.81 (2.44)	0.0108
Δ vs. Baseline		−2.29 (2.18) (−34.33%)		−1.52 (2.22) (−21.71%)			−3.48 (2.47) (−59.38%)		−2.22 (2.07) (−38.01%)	

ITT: intent-to treat; MS: multiple sclerosis; NRS: numerical rating scale; SD: standard deviation.

(2.37) with THC:CBD spray (nabiximols) and −1.85 (2.29) with placebo ($p = 0.1284$). Corresponding values in the EDSS score ≥6 subgroup were −3.49 (2.41) and −1.98 (2.02), respectively ($p = 0.003$). In the subgroup with more severe disability, differences between active treatment and placebo were significant also at weeks 4 and 8 (Table 5).

Mean pain NRS scores were reduced with THC:CBD oromucosal spray (nabiximols) compared with placebo in patients with spasticity 0-10 NRS scores of ≤6 or >6 at randomization, with statistically significant differences in the spasticity NRS score >6 subgroup. In the spasticity NRS score ≤6 subgroup, mean (SD) changes in pain 0-10 NRS scores between randomization and week 12 of treatment were −2.36 (1.51) with THC:CBD spray (nabiximols) and −2.07 (1.54) with placebo ($p = 0.4979$). Corresponding values in the spasticity score >6 subgroup were −3.31 (2.67), and −1.85 (2.35), respectively ($p = 0.0008$). In the subgroup with severe spasticity, differences between active treatment and placebo were significant also at weeks 4 and 8 (Table 6).

Mean pain NRS scores were reduced significantly with THC:CBD oromucosal spray (nabiximols) compared with placebo irrespective of MS spasticity duration. In the patient subgroup with spasticity duration ≤5 years, mean (SD) changes in pain 0-10 NRS scores between randomization and week 12 of treatment were −2.29 (2.18) with THC:CBD spray (nabiximols) and −1.52 (2.22) with placebo ($p = 0.0307$). Corresponding values in the patient subgroup with spasticity duration >5 years were −3.48 (2.47) and −2.22 (2.07), respectively ($p = 0.0108$). In each spasticity duration subgroup, differences between active treatment and placebo were significant also at weeks 4 and 8 (Table 7).

4. Discussion

In 2014, as part of a scheduled re-evaluation of newly-approved medicines three years after their commercialization, German authorities requested proof that add-on THC:CBD oromucosal spray (nabiximols) was more effective in providing symptomatic relief of MS spasticity than readjusting doses and combinations of classical oral antispasticity medications. This request led to the design and implementation of the SAVANT study which applied an enriched-design methodology to compare THC:CBD oromucosal spray (nabiximols) and placebo in patients with moderate to severe MS spasticity who had not gained adequate relief from at least two optimized standard antispasticity drugs (i.e. baclofen, tizanidine, dantrolene) [13]. Among patients who showed an initial capacity to respond to THC:CBD spray (nabiximols) during the 4-week single-blind initial treatment phase in accordance with EU prescribing information [8], the proportion of patients with a clinically relevant response ($\geq$30% NRS improvement) after 12 weeks of double-blind treatment was significantly greater for the group randomized to active medication than placebo (77.4 vs. 32.1%; $p < 0.0001$).

Similar to observations in other randomized controlled studies of THC:CBD oromucosal spray (nabiximols) for treating resistant MS spasticity [9–12], and consistent with the known heterogeneity of the MS clinical phenotype [1], patients in the SAVANT study had varying presentations of disease and related symptoms, prompting questions as to whether certain baseline clinical characteristics might influence treatment response. Identifying patients likely to respond to THC:CBD spray (nabiximols) before starting treatment would be beneficial in terms of time and cost efficiencies, managing patients' expectations, and limiting drug exposure in patients who are unlikely to benefit. Our post hoc analysis of SAVANT study data was designed to determine whether the efficacy of THC:CBD spray (nabiximols) was similar among subgroups defined by disability status (EDSS score $<$6 or $\geq$6), spasticity severity (spasticity 0-10 NRS score $\leq$6 or $>$6), and spasticity duration ($\leq$5 or $>$5 years) at the time of randomization to double-blind treatment.

Mean spasticity 0-10 NRS score evolution during 12 weeks' double-blind treatment with THC:CBD oromucosal spray (nabiximols) or placebo showed that the treatment effect of active medication on MS spasticity severity was significantly greater than that of placebo for subgroups defined by baseline disability status or spasticity duration. The effect of active treatment was also significantly superior to that of placebo in patients with severe spasticity (0-10 NRS score $>$6) at randomization, reaching a 49% reduction in the baseline mean NRS score. Patients with moderate spasticity (0-10 NRS score of 4 to $\leq$ 6 at randomization) treated with THC:CBD spray (nabiximols) achieved a 51% reduction in the baseline mean NRS score, although the difference was not statistically significant compared with placebo-allocated patients. The lack of significance is due in part to the small size of this subgroup ($n = 14$), which is the main limitation of our analysis, and also to the relatively high placebo effect in the moderate spasticity subgroup.

Mean pain 0–10 NRS score evolution during 12 weeks' treatment with THC:CBD oromucosal spray (nabiximols) or placebo showed that the treatment effect of active medication on pain severity significantly exceeded that of placebo irrespective of spasticity duration. The treatment effect of active treatment also significantly exceeded that of placebo in patients with greater disability (EDSS score $\geq$6) and more severe spasticity (0-10 NRS score $>$6) at baseline.

In both the spasticity and pain analyses, the superior treatment effects of THC:CBD oromucosal spray (nabiximols) versus placebo, if evident by week 4 of treatment, were maintained at week 8 and week 12 of treatment.

Interestingly, MS spasticity duration at baseline did not differentially affect the ability of active treatment to alleviate spasticity and pain. MS has a profoundly heterogeneous clinical course [14] and, at the individual level, impairment severity does not always correlate directly with symptom prevalence or duration [2]. It is noteworthy that baseline disability status did not differentially affect the ability of THC:CBD oromucosal spray (nabiximols) to alleviate spasticity, whereas the effects of active treatment on pain relief were superior compared with placebo in the subgroup with greater baseline disability. In particular, for ambulatory patients (EDSS $<$ 6), the association between disability status and spasticity severity can be expected to be stronger than that between disability status and pain severity. Furthermore, aside from small sample size considerations, we were not surprised to observe that the ability of THC:CBD spray (nabiximols) to alleviate spasticity and pain was more pronounced in patients with higher MS spasticity scores at baseline (0-10 NRS score $>$6) since these patients have greater scope for improvement. Notwithstanding, patients with moderate resistant MS spasticity also deserve effective symptomatic management. The failure of patients with resistant MS spasticity to respond adequately to conventional oral antispasticity medications is a genuine clinical challenge, and these patients may stand to

benefit most from alternative options such as THC:CBD spray (nabiximols). In this post hoc analysis, we have shown that the benefit of add-on THC:CBD spray (nabiximols) extends to several subgroups within the target population of patients with resistant MS spasticity.

5. Conclusions

The analyses indicate that add-on THC:CBD oromucosal spray (nabiximols) provides consistent additional relief from spasticity and pain symptoms despite already-optimized underlying oral antispasticity therapy across key subgroups within the target population of patients with resistant MS spasticity. Spasticity (0-10 NRS) scores were reduced by −2.9 to −3.7 points and pain (0-10 NRS) scores were reduced by −2.3 to −3.5 points independently of patients' MS spasticity duration at baseline. Among patients with resistant MS spasticity, disability status (EDSS score) differentially affected improvement in pain but not spasticity during double-blind treatment with THC:CBD spray (nabiximols) or placebo. THC:CBD oromucosal spray (nabiximols) relieved spasticity and pain numerically relative to placebo in patients with moderate spasticity (0-10 NRS score $\leq$6) at baseline, and its effects relative to placebo were statistically significant in patients with severe spasticity (0-10 NRS score $>$6) at baseline.

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