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A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols* (Sativex®), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis

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Background: Spasticity is a disabling complication of multiple sclerosis, affecting many patients with the condition. We report the first Phase 3 placebo-controlled study of an oral antispasticity agent to use an enriched study design.

Methods: A 19-week follow-up, multicentre, double-blind, randomized, placebo-controlled, parallel-group study in subjects with multiple sclerosis spasticity not fully relieved with current antispasticity therapy. Subjects were treated with nabiximols, as add-on therapy, in a single-blind manner for 4 weeks, after which those achieving an improvement in spasticity of ≥20% progressed to a 12-week randomized, placebo-controlled phase.

Results: Of the 572 subjects enrolled, 272 achieved a ≥20% improvement after 4 weeks of single-blind treatment, and 241 were randomized. The primary end-point was the difference between treatments in the mean spasticity Numeric Rating Scale (NRS) in the randomized, controlled phase of the study. Intention-to-treat (ITT) analysis showed a highly significant difference in favour of nabiximols ($P = 0.0002$). Secondary end-points of responder analysis, Spasm Frequency Score, Sleep Disturbance NRS Patient, Carer and Clinician Global Impression of Change were all significant in favour of nabiximols.

Conclusions: The enriched study design provides a method of determining the efficacy and safety of nabiximols in a way that more closely reflects proposed clinical practice, by limiting exposure to those patients who are likely to benefit from it. Hence, the difference between active and placebo should be a reflection of efficacy and safety in the population intended for treatment.

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*Sativex does not yet have an INN, but the product does have a US Adopted Name (USAN): 'nabiximols'. Therefore, we use 'nabiximols' in preference to the full product name throughout the text.

Trial registration: The details of this study were registered on clinicaltrials.gov (Ref. NCT00681538).

Introduction

Multiple sclerosis (MS) is the commonest physically disabling neurological condition in young adults, with a prevalence between 50 and 200 per 100 000, depending on ethnic and geographical factors [1,2]. Multifocal demyelination and axonal loss, thought to be via an autoimmune mechanism, result in the dysfunction of

the central nervous system (CNS) and lead to the production of symptoms such as pain, spasticity, spasms and bladder dysfunction. Spasticity (stiffness) is a common symptom of MS and occurs, as the disease evolves, in more than 60% of people with MS (PwMS) [3,4]. Spasticity is usually associated with painful spasms, sleep disturbance and pain, and it contributes to reduced mobility, increasing the burden of disease for both PwMS and their caregivers [5]. Current oral medication for spasticity includes baclofen, tizanidine, dantrolene, benzodiazepines and anticonvulsants [3,5]. Despite the widespread use of these agents, the evidence base for their use is weak and the relief they provide from spasticity is modest [3,5]. There is a clear need for new therapeutic agents to treat spasticity.

In a clinical trials setting, it can be problematic showing clear-cut efficacy in a population of patients where a proportion may lack the capacity to respond to treatment. The 'conventional' parallel-group randomized, controlled study identifies the average improvement seen in a group of patients, but may tell us little about the clinical relevance of that average improvement.

Therefore, to investigate the efficacy and safety of Sativex in a study design that better reflects normal clinical use, this study used an enriched enrolment design, in which only those participants who had demonstrated the capacity to respond to treatment were eligible for randomization.

Cannabis sativa L. contains 60 or more cannabinoids, the most abundant of which are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) [6]. Both of these have a pharmacology which suggests they may be useful in the relief of spasticity [7,8].

The endogenous cannabinoids (anandamide, 2-arachidonoyl glycerol [2-AG]) act primarily via specific cannabinoid receptors (CBr): CB_1 receptors are predominantly distributed in the CNS; CB_2 receptors are located both in the CNS and extensively in the periphery (especially the immune system) [8]. Both endogenous and exogenous cannabinoids have been shown to have a therapeutic effect in the animal models of MS spasticity. [9] through effects primarily at the CB1r. However, it has also been shown that not all of their effects are mediated through the CB1r.

The principal pharmacological effects of THC include analgesia, muscle relaxation, anti-emesis, appetite stimulation and psychoactivity. CBD has anticonvulsant, muscle relaxant, anxiolytic, neuroprotective, antioxidant and antipsychotic activity and has been shown to reduce the anxiogenic and psychoactive effects of THC [8,10].

Nabiximols (Sativex; GW Pharma Ltd, Salisbury, UK) contains THC + CBD at a nearly 1:1 fixed ratio and is described as an endocannabinoid system modulator. It is derived from fully standardized chemotypes of *Cannabis sativa* L. plants developed to produce high and reproducible yields of the two principal cannabinoids (THC and CBD), with minor amounts of other cannabinoids and terpenes, and prepared in a solution containing ethanol, propylene glycol and peppermint oil flavouring for oromucosal use through a sealed pump device.

Earlier studies using nabiximols showed a significant improvement in the patient-reported severity of spasticity in patients with MS [11,12]. In addition, a meta-analysis of three Sativex studies has demonstrated the benefit in this indication [13], using a validated 0–10 Numerical Rating Scale (NRS) [14,15]. An approximate 20% improvement (18%) in the patient self-reported severity of spasticity has been shown to be the minimum clinically important difference, with a 30% improvement representing 'much improved' [14].

The study reported here evaluated the efficacy and safety of Sativex compared with placebo on the severity of spasticity experienced by patients with MS who had insufficient benefit from their existing antispasticity medication and who had shown the capacity to respond to treatment. Active treatment or placebo was administered as add-on therapy to the ongoing oral antispasticity medications.

Methods

This was a 19-week duration study: 1 screening week, 16 treatment weeks, plus 2 weeks end of treatment follow-up period, and was conducted in two phases (Phases A & B) in 51 study sites in Europe (18 centres in the United Kingdom, 11 in Spain, 10 in Poland, 8 in the Czech Republic and 5 in Italy). The study was approved by the relevant Institutional Review Board or Ethical Committee in each of the countries; it was conducted according to Good Clinical Practice guidelines.

In this enriched study design, Phase A was a preliminary, single-blind, 4-week treatment period to identify subjects with a response to nabiximols. During this period, the subjects were not aware whether they were taking placebo or Sativex, although the investigator was aware that all subjects were allocated to treatment with Sativex. Response was assessed using a validated self-reported 0–10 point NRS. Those with at least a 20% reduction in mean NRS spasticity score between screening and the end of the 4-week Phase A treatment were classified as responders and were eligible for entry into Phase B. Subjects who did not attain at least a 20% improvement took no further part in the study.

Phase B was a 12-week double-blind, randomized, placebo-controlled, parallel-group study with visits at 4-week intervals. All subjects underwent a final follow-up visit 2 weeks after completion of treatment. This follow-up visit was aimed at identifying any safety issues associated with the withdrawal of treatment.

The level of spasticity, spasm frequency and sleep disruption were collected each day during the entire study using the NRS via an Interactive Voice Response System (IVRS). In addition, study medication dosing data were also recorded via IVRS throughout the Phases A and B. Assessments of other secondary and functional measures of spasticity, safety and tolerability, quality of life (QoL) and mood assessments were also collected throughout the study.

Assessments were made at screening, baseline, weeks 4 (end of Phase A), 8, 12, 16 (the end of treatment, Phase B) and at the end of the study (week 18) or earlier if subjects withdrew.

Inclusion and exclusion criteria

Study entry inclusion criteria

Eligible subjects had MS of any subtype for at least 6 months, with spasticity because of MS for at least 3 months, which was not wholly relieved with current antispasticity medication. Antispasticity agents and/or disease-modifying medications were maintained at a stable dose for 30 days prior to and throughout the study.

Subjects had to have at least moderately severe spasticity, as defined by a score of ≥4 using a single spasticity 0–10 severity NRS at screening. Each treating physician was asked to ensure at the screening visit that the patients were able to understand the meaning of spasticity.

Phase B inclusion criteria (randomization eligibility)

At week 4, eligible patients who had no major protocol violations were offered the opportunity to continue in Phase B of the study. To qualify for randomization in the placebo-controlled phase of the study (Phase B), subjects must have had at least a 20% reduction in their NRS spasticity score, an improvement that has shown to predict a clinically significant response (improvement of 30% or more) in a previously conducted clinical trial [16], had no new antispasticity or disease-modifying medication introduced and no alterations to dosage of antispasticity or disease-modifying medication made throughout Phase A. In addition, the treatment regimen of all medications that might have affected the subject's spasticity was required to remained stable in Phase A, and in the opinion of the investigator, the subject must have remained blind to treatment allocation throughout Phase A.

Study exclusion criteria

Any subjects who had a concomitant disease or disorder that had spasticity-like symptoms or that may have influenced the subject's level of spasticity, or who had a medical history that suggested that relapse/remission was likely to recur during the study which was expected to influence the subject's spasticity, were excluded. Any subjects who were using or had used cannabis or cannabinoid-based medications in the 30-day period prior to study entry were excluded, as well as any subject with a concurrent history of significant psychiatric, renal, hepatic, cardiovascular or convulsive disorders was also excluded, as were subjects with known or suspected history of alcohol or substance abuse, diagnosed-dependence disorder or current non-prescribed use of any prescription drug.

Treatment groups and doses

Study medication was delivered using a pump action oromucosal spray. Each 100-μl actuation of active medication delivered 2.7 mg THC and 2.5 mg CBD to the oral mucosa. Subjects were restricted to a maximum of 12 sprays in any 24-h period. The subjects self-titrated during the first ten treatment days, up-titrating through a pre-defined escalation scheme to their optimal dose, based on efficacy and tolerability.

Study end-points

Efficacy end-points

The primary efficacy end-point was the change in spasticity Numerical Rating Scale (0–10 NRS) from the point of randomization to the end of treatment. Hence, the primary efficacy end-point and the key secondary efficacy end-points refer only to those patients who were randomized. A number of secondary efficacy end-points were also assessed.

Safety end-points

In both Phases A and B, safety and tolerability were assessed at each visit, and the Beck Depression Inventory II was administered at weeks 0, 4 and 16 to detect mood changes. Physical examination, including oral inspection, was performed every 4 weeks.

Statistical methods

Single-blind phase (Phase A)

For Phase A, data were summarized at each time-point using descriptive statistics. IVRS data were summarized using means over consecutive 7-day intervals and during the last 7 days on treatment.

Double-blind phase (Phase B)

The baseline spasticity NRS value was the mean of the last 7-day scores (end of week 4) of Phase A

treatment. The variable for analysis was the change in mean spasticity NRS score from baseline to the end of treatment assessed as the mean NRS spasticity score during week 16 (last week of the Phase B treatment period). The primary analysis was performed in the intention-to-treat (ITT) population over the 12-week post-randomization period. The change from double-blind baseline to end of study was assessed using a linear model (ANCOVA) with the baseline value as covariate and randomized treatment, country and ambulatory status at baseline as factors. Subjects who did not have any evaluable post-randomization efficacy data were excluded from the analysis.

All statistical comparisons between treatments used two-sided statistical tests and a significance level of 5%.

All randomized subjects who received at least one dose of study medication were included in the safety analyses.

Sample size

Based upon previous studies, it was estimated that this study would result in a difference in the primary endpoint between active and placebo subjects of at least 0.75 points in the NRS, with a standard deviation (SD) of approximately 1.6 points. For a significance level of 5% and 90% power, a total of 194 evaluable subjects (97 in each group) were needed. Allowing for 20% of randomized subjects to be non-evaluable, 244 subjects (122 in each group) were required to be randomized into Phase B. It was estimated that 50% of the subjects enrolled in Phase A of the study would be identified as potential responders. And therefore, approximately, 488 subjects would need to enter Phase A of the study.

Results

A summary of breakdown of subjects enrolled in the overall study is shown in Fig. 1, with study population demographics displayed in Table 1. The demographics of the randomized population are very similar to those of the population who were not eligible for randomization. The mean duration of multiple sclerosis was in excess of 12 years, and the mean duration of spasticity was in excess of 7 years. There were no notable differences in the characteristics of those subjects randomized to nabiximols compared with those randomized to placebo (data not shown). During Phase A, subjects had a mean daily number of 6.9 (SD = 1.78) sprays. In Phase B, the mean daily number of sprays taken by the active treatment group was 8.3 (SD = 2.43) compared with 8.9 (SD = 2.31) by the placebo group.

Concomitant medication

The majority of subjects in both phases of the study were taking antispasticity medication with baclofen, being the most common medication taken. A full list of the antispasticity medications being taken during the randomized phase of the study is presented in Table 2. As is to be expected, in this patient population, most patients (85%) were taking concomitant medication for other reasons than spasticity. The most frequently taken classes of medicine were antidepressants (>32%), analgesics (>30%), proton pump inhibitors (16%), urinary antispasmodics (20%) and lipid-lowering agents (>10%).

Primary analysis: spasticity 0–10 NRS

Phase A

The mean change in spasticity 0–10 NRS score at the end of the 4-week single-blind treatment with nabiximols was a decrease (improvement) of 3.01 (±SD = 1.38) points (from a baseline score of 6.91 ± 1.25 to a score of 3.9 ± 1.51 points) (Fig. 2). For those subjects who were not randomized (n = 331), the percentage improvements from baseline were as follows:

less than 5% improvement – 50%;
between 5% to less than 10% improvement – 14%
between 10% to less than 15% improvement – 16%
between 15% to less than 20% improvement – 11%
more than 20% improvement but not eligible for randomization for other reasons – 9%

Phase B

Over the course of the 12-week double-blind, randomized phase, the mean spasticity score had further improved in the active treatment group by 0.04 units, from a baseline score of 3.87 points. In the placebo group, there was a mean deterioration of 0.81 from a baseline score of 3.92 points. The estimated treatment difference between the two groups in mean spasticity NRS was 0.84 points (95% CI: −1.29 to −0.40). This difference was highly statistically significant (P = 0.0002).

Secondary end-points

The number of responders (defined as at least a 30% improvement in spasticity from the screening baseline) in the active treatment group was significantly higher than in the placebo group (74% vs. 51%: odds ratio 2.73 [95% CI 1.59 to 4.69] : P = 0.0003).

A total of 56 subjects (45%) who received Sativex were classed as >50% responders compared with 39

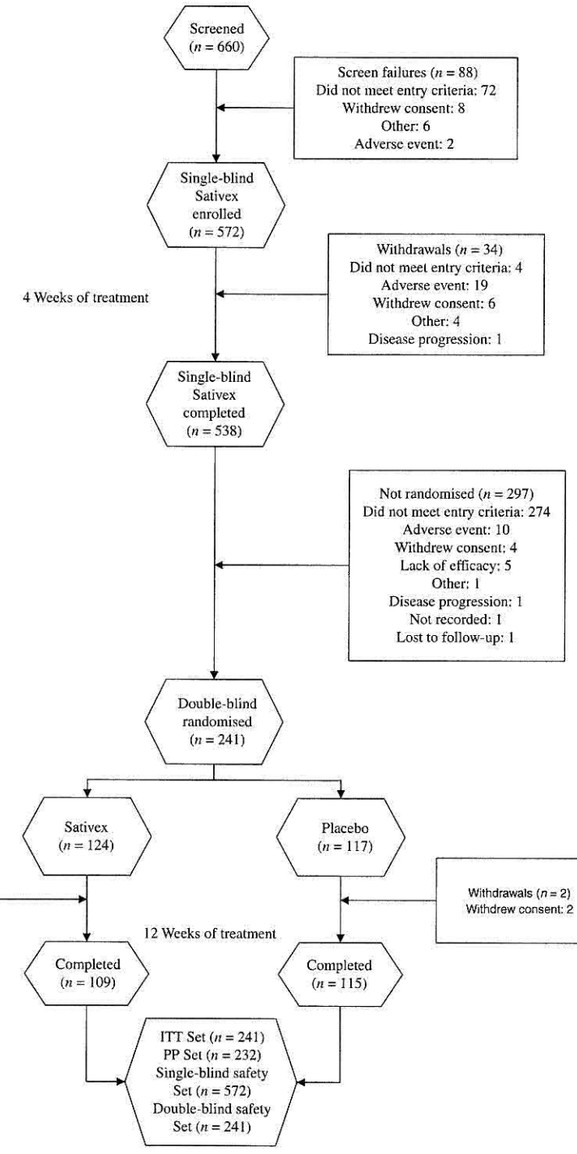

Figure 1 Disposition of subjects.

subjects (33%) on placebo. This approached statistical significance (P = 0.061).

Amongst the other secondary efficacy assessments, Sativex was significantly superior to placebo for spasm frequency (P = 0.005), sleep disruption (P < 0.0001), Barthel Activities of Daily Living (P = 0.0067), Physician Global Impression of Change (P = 0.005), Subject Global Impression of Change (P = 0.023) and Carer Global impression of Change in Function (P = 0.005). All other secondary efficacy measures were in favour of Sativex, without reaching statistical significance. The results of the primary and secondary efficacy analyses are shown in Table 3.

Table 1 Demographics and baseline characteristics for all subjects who completed Phase A of the study

	Non-randomized (n = 331)	Randomized to double-blind phase (Phase B) (n = 241)	Total (n = 572)
	No. of subjects (%)		
Gender			
Male	129 (39)	96 (40)	225 (39)
Female	202 (61)	145 (60)	347 (61)
Ethnic origin			
White/caucasian	330 (100)	241 (100)	571 (100)
Other	1 (<0.05)	0	1 (<0.5)
Previous cannabis use in the last year	43 (13)	44 (18)	87 (15)
Non-ambulatory	67 (20)	65 (27)	132 (23)
	Mean (SD)		
Age (years) (range)	49.1 (9.85) (28.0, 76.0)	48.6 (9.33) (23.3, 69.6)	48.9 (9.63) (23.3, 76.0)
BMI (kg/m^2) (range)	25.1 (4.73) (16.4, 41.7)	25.6 (4.91) (14.9, 45.1)	25.3 (4.80) (14.9, 45.1)
Duration of MS (years) (range)	12.3 (7.49) (0.5, 38.7)	12.6 (7.88) (1.5, 42.4)	12.4 (7.66) (0.5, 42.4)
Duration of spasticity (years) (range)	7.4 (5.54) (0.2, 32.2)	7.7 (6.27) (0.5, 40.4)	7.5 (5.86) (0.2, 40.4)
EDSS score* (range)	6.0 (1.40) (1.0, 9.0)	6.0 (1.45) (1.5, 9.0)	6.0 (1.42) (1.0, 9.0)
Baseline spasticity NRS (range)	6.8 (1.35) (3.0, 10.0)	7.0 (1.39) (4.0, 10.0)	6.9 (1.37) (3.0, 10.0)

MS, multiple sclerosis, NRS, Numeric Rating Scale.

Table 2 Summary of all antispasticity medication being used by the randomized subjects

Medication class/name	Sativex (%)	Placebo (%)	Total (%)
Adamantane derivatives	17 (14)	15 (13)	32 (13)
Benzodiazepine-related derivatives	23 (18)	30 (25)	53 (22)
Dantrolene	1 (1)	0	1 (<0.5)
Naltrexone	0	1 (1)	1 (<0.5)
Anti-epileptics	37 (29)	21 (18)	58 (24)
Centrally acting agents	87 (70)	90 (77)	177 (73)
Baclofen	66 (53)	73 (62)	139 (58)
Tizanidine	20 (16)	20 (17)	40 (17)
Tolperisone	1 (1)	0	1 (<0.5)
Others	2 (2)	0	2 (1)

Safety and tolerability

All adverse events (AEs) experienced in subjects during both Phases A and B in the study are displayed in Table 4. Assessment of mood change using the Beck Depression Inventory showed no differences between nabiximols and placebo (data not shown). During Phase B of the study, the overall adverse event rate was similar between nabiximols and placebo, with no single event occurring at a rate greater than 10% in either group (urinary tract infection in placebo). The most common adverse events in the nabiximols group were vertigo, fatigue, muscle spasms and urinary tract infection.

Discussion

This study has shown Sativex to improve spasticity in patients who had failed to respond adequately to other antispasticity medications and who had undergone a successful 4-week 'trial of therapy'. The results of the self-reported primary end-point of the Numeric Rating Scale were confirmed by a panel of secondary measures including the patient's assessment of their sleep quality, the quantitative assessment of number of daily spasms, the independent impressions of the caregiver and of the physician as well as the functional measure of the Barthel Activities of Daily Living Index.

The endocannabinoid system has been shown to control spasticity in the animal models of the disease [9,17] and endogenous and exogenous cannabinoids have been shown to improve spasticity in such models, thereby providing a sound pharmacological basis for the treatment of spasticity with cannabinoids. In addition to the *in vivo* evidence, cannabinoids have been shown to be effective in the relief of spasticity in subjects with MS in a number of clinical trials [11,12,18–22]. All of these studies have used a conventional parallel-group, placebo-controlled, randomized study design and have included all subjects who met the entry criteria. Such study designs only provide information about the average response to treatment, where the average response includes not only the effect of the medicine in those who respond to it but also in those who do not respond. This tells us relatively little about the effectiveness of the medicine in a clinical setting, where those patients who fail to respond would not normally continue treatment. And in a patient population of this type with very chronic disease and a history of failure to respond adequately to existing therapy, it is to be expected that a proportion of patients may lack the capacity to respond to a new therapeutic agent. In the setting where a proportion of patients do not respond to treatment, the conventional randomized controlled trial may therefore underestimate the 'real' effect of treatment.

This is the first report of an enriched study design of this sort being used to assess the efficacy and safety of a treatment for spasticity in people with MS. The pre-

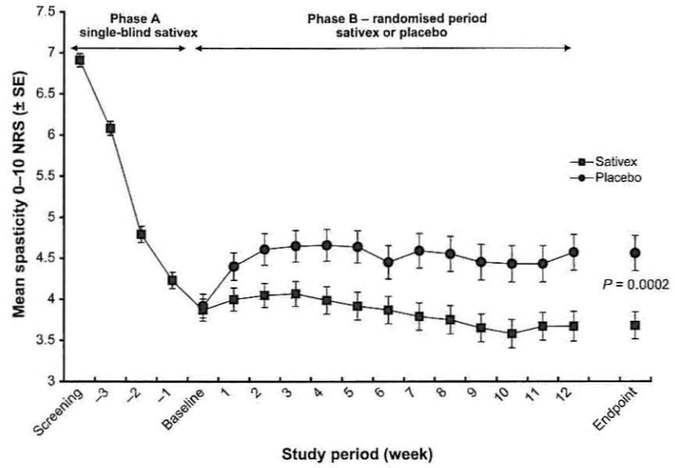

Figure 2 0–10 Numeric Rating Scale (NRS) spasticity scores during the study (intention-to-treat analysis).

Table 3 Summary of primary and secondary efficacy results (Phase B), comparing mean values of Nabiximols vs placebo, from baseline to end of treatment

	Summary of primary and secondary efficacy end-points – double-blind phase (Phase B)			
Variable	Nabiximols (mean)	Placebo (mean)	Treatment difference	P-value
Spasticity NRS	−0.19	0.64	**−0.83**	**0.0002**
30% responder	**0.74**	**0.51**	**0.23**	**0.0003**
50% responder	0.45	0.33	0.12	0.0612
Spasm frequency	**−0.03**	**2.56**	**−2.53**	**0.005**
Sleep disruption NRS	**−0.13**	**0.75**	**−0.88**	**<0.0001**
Modified Ashworth scale	0.08	1.83	−1.75	0.094
Motricity index				
Arm	−10.50	−8.58	−1.92	0.630
Leg	−3.24	−4.21	0.97	0.439
Timed 10-m walk	−0.13	3.22	−3.34	0.069
EQ-5D Health state index	−0.03	−0.05	0.02	0.284
EQ-5D Health status VAS	−1.99	−3.24	1.24	0.564
SF-36				
Physical functioning	0.30	0.76	−0.46	0.782
Role physical	−0.31	0.98	−1.30	0.658
Bodily pain	−0.05	−5.06	5.01	0.060
General health	1.20	−0.12	1.32	0.442
Vitality	−1.17	−3.35	2.19	0.306
Social functioning	−0.97	−0.32	−0.65	0.840
Role emotional	−1.26	1.53	−2.78	0.343
Mental health	−2.20	−2.94	0.74	0.683
	95% confidence interval			
	Lower	Upper		
Barthel ADL index	**1.223**	**3.446**	**2.04**	**0.0067**
SGIC	**1.075**	**2.698**	**1.70**	**0.023**
CGIC – impression of function	**1.297**	**4.443**	**2.40**	**0.005**
CGIC – Ease of transfer	0.973	3.301	1.79	0.061
PGIC	**1.232**	**3.112**	**1.96**	**0.005**

NRS, Numeric Rating Scale.

randomization, blinded exposure to active medication allowed for the identification of a subgroup of patients who had exhibited the capacity to respond to treatment, and it was only this subgroup of subjects who were then randomized. In this study, this run-in period was single-blind. The response seen during the single-blind exposure period does not necessarily represent a response to Sativex, but rather shows that the patient has the capacity to respond. In this way, subjects lacking the capacity to respond were not randomized and were therefore not exposed to the hazards of continued treatment. The purpose of keeping the subjects blind to treatment during the initial 4 weeks of the study was to try and reduce the impact of any expectation that the participant might have about the efficacy and/or safety of the active drug and to reduce the potential for unblinding during the subsequent randomized period. To provide a further safeguard against the prospect of unblinding, those subjects who had improved during the run-in period were only randomized if the investigator believed that they remained blind to treatment allocation. Whilst the judgement of the investigator in this regard may not be wholly objective, and this may be a theoretical weakness of the study design, nonetheless we believe that this design feature is likely to help maintain the blind to treatment allocation. Subjects were not asked to guess whether they had been taking active drug or placebo at any stage during the study; the response to this question may better identify whether the active medication is effective than whether patients have been unblinded [23].

The enriched study design has recently been discussed at length by McQuay *et al.* [24], in the setting of chronic pain. It better reflects the way that symptomatic treatments are used in a clinical setting, where patients who do not respond to a medicine, or who find it intolerable, are unlikely to continue treatment for a prolonged period. Indeed, it is not desirable for such non-responder patients to continue treatment because they will only be exposed to the hazards of the medicine and not the benefits. This approach reflects good clinical medical practice. In this way, it also better reflects the kind of efficacy that is likely to be seen in a 'real-world' setting. Furthermore, the run-in phase, even though it occurs prior to randomization, can provide useful information about the heterogeneity of response and the features of response more likely to be seen in clinical practice. There is no reason to suppose that this type of study design eliminates or even reduces the placebo response. In fact, by including only those patients who have demonstrated the capacity to respond, it is more likely to enhance the placebo response.

The threshold for identifying a subject as eligible for randomization was defined as being at least a 20% improvement in the spasticity NRS from baseline. This was based on analyses of previously reported studies where the minimal clinically important difference (MCID) in the spasticity NRS was found to be approximately 18% [14]. The same analysis identified a 30% improvement from baseline as the threshold for identifying a responder. It is of note that the NRS for spasticity behaves in a similar way to that for chronic pain, at least with regard to the level of improvement that is clinically relevant. It has also been shown in the setting of a randomized clinical trial that a subject who achieves a 20% improvement after 4 weeks of treatment is highly likely to achieve a 30% improvement in longer-term exposure [16].

As with previous studies with Sativex in spasticity because of MS, the MS population enrolled in this study had advanced disease with spasticity that was resistant to treatment with current oral antispasticity agents. Subjects exhibited severe levels of spasticity at study entry (mean score >6.5 on a spasticity 0–10 NRS) despite ongoing treatment with the best available antispasticity treatments such as baclofen, tizanidine and benzodiazepines. Few subjects dropped out during this study – indicating that compliance and tolerability were good. The withdrawal rate of only 7% is low in studies in this indication. Of the 17 randomized subjects who discontinued treatment early, 15 of them were on nabiximols (and these withdrawals were mainly because of adverse events or withdrawal of consent (n = 11)). The high subject retention rate in the study may be reflective of a more cautious dose titration regimen than was used in previous studies, which is also consistent with the lower rate of adverse events observed in this study than has been reported previously with nabiximols.

The estimated treatment difference between the two groups as measured using NRS was 0.84 points from a baseline severity of 3.89 for the nabiximols group and 3.92 for the placebo group. This difference was greater than the 0.75 units difference that had been anticipated during the sample size calculations. The majority of the spasticity-related secondary end-points lend objective and independent support to the clinical relevance of the difference seen between nabiximols and placebo in the subjective NRS measure of the primary end-point. The high degree of consistency between the NRS and secondary variables such as spasm count and sleep disturbance also provides evidence of internal consistency and reassurance that the subjective NRS subject-rated assessment of efficacy of Sativex on the relief of spasticity is robust. The consistency of the Global Impression of Change scales data between subject, carer and physician ratings of change lend further objective support to the subject self-rated outcomes. Further, the

Table 4 Adverse events occurring in at least 3% of the study population – shown during Phase A for all subjects, and in Phase B for those randomized to nabiximols and to placebo

System organ class Preferred term	Phase A (n = 572) N (%)	Phase B Nabiximols (n = 124) (%)	 Placebo (n = 117) (%)
Subjects with at least one AE	**268 (46.9)**	**66 (53)**	**57 (49)**
Ear and labyrinth disorders	**22 (3.8)**	**7 (6)**	**1 (1)**
Vertigo	21 (3.7)	7 (6)	1 (1)
Gastrointestinal disorders	**75 (13.1)**	**18 (15)**	**12 (10)**
Dry mouth	24 (4.2)	4 (3)	1 (1)
Nausea	23 (4.0)	5 (4)	2 (2)
Diarrhoea	8 (1)	3 (2)	6 (5)
Abdominal pain (upper)	4 (1)	4 (3)	0
General disorders and administration site conditions	**80 (14.0)**	**18 (14)**	**9 (8)**
Fatigue	34 (5.9)	6 (5)	1 (1)
Infections and infestations	**40 (7)**	**19 (15)**	**26 (22)**
Urinary tract infection	16 (3)	9 (7)	12 (10)
Naso-pharyngitis	8 (1)	4 (3)	3 (3)
Musculo-skeletal and connective tissue	**27 (5)**	**18 (15)**	**18 (15)**
Muscle spasms	6 (1)	7 (6)	8 (7)
Back pain	1 (0.2)	5 (4)	4 (3)
Pain in extremity	1 (0.2)	0	5 (4)
Nervous system disorders	**148 (25.9)**	**19 (15)**	**15 (13)**
Dizziness	80 (14.0)	4 (3)	0
Somnolence	29 (5.1)	4 (3)	1 (1)
Headache	13 (2)	2 (2)	5 (4)
Muscle spasticity	11 (2)	3 (2)	4 (3)
MS relapse	4 (1)	4 (3)	1 (1)
Psychiatric disorders	**47 (8)**	**13 (11)**	**7 (6)**
Euphoric mood	8 (1)	4 (3)	1 (1)

MS, multiple sclerosis; bold items indicate the total numbers of subjects with an AE by System Organ Class (SOC) according to the MedDRA classification of AEs.

improvements in functional capacity, as assessed by the Barthel Index, help to interpret the overall self-reported findings and suggest that the patients' self-reported outcome is associated with improvements in function. Such functional improvements may have a significant impact on both the PwMS's and carer's quality of life.

Another means of assessing the clinical relevance of the difference between active and placebo is the responder rate. Previous studies suggested that between 35 and 40% of subjects will see a 30% or more improvement in spasticity when taking nabiximols. In this study, 74% of randomized subjects showed an improvement of 30% or more after a further 12 weeks of treatment on Sativex, compared with 51% of subjects on placebo. This high responder rate was seen in subjects who had exhausted other available oral antispasticity medications.

The study medication was generally well tolerated in this study. The AE profile during Phase A of the study was better than that observed in other clinical studies with nabiximols [11,12,16]. The AE incidence was even lower in the randomized phase of the study. This tolerability is further reflected in that only 3% of subjects withdrew because of AEs in either Phase A or Phase B. There were only two treatment-related serious adverse events, and both resolved rapidly upon cessation of treatment. There was no evidence for any generalized alteration of mood.

In summary, in this enriched study, the results for the primary end-point were statistically significantly in favour of nabiximols. The analysis of secondary end-points confirm that nabiximols, taken as adjunctive therapy to existing oral antispasticity medications, can produce clinically relevant improvements in spasticity in a considerable proportion of MS subjects with refractory spasticity in a relatively short space of time. Sativex was generally well tolerated; the AE profile improved in comparison with previous studies and no new safety signals were identified. The use of an enriched study design has added clarity by identifying the magnitude of the benefit that derives from treatment with nabiximols in responder subjects. This means of identifying those subjects who are likely to gain a good response – a trial of therapy – is simple and familiar to clinicians.

Given the safety and tolerability of Sativex and the size of potential benefit in an easily identified subset of responders, initiating refractory subjects on a therapeutic trial of treatment for a limited period of 4 weeks appears to be a useful therapeutic approach in the management of spasticity in PwMS.

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