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


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Keywords: cannabidiol, cannabinoids, delta-9-tetrahydrocannabinol, endocannabinoid system, multiple sclerosis, nabiximols, Sativex, spasticity

Received 30 July 2010
Accepted 29 November 2010

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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In clinical trials, 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. Sativex 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 (CBs). CB receptors are predominantly distributed in the CNS; CB receptors are located both in the CNS and extensively in the periphery (e.g. in 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 (Sanofi, OW Pharma Ltd, Salisbury, UK) contains THC + CBD at a nearly 1:1 fixed ratio and is described as an endo-cannabinoid system modulator. It is derived from fully standardized chemicals 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 cannabinoid and nonpsychotropic constituents. It is prepared in a solution containing ethanol, propylene glycol and emollient oil favouring for ophthalmic 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 effectiveness of the medication in the reduction of the number of spastic 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 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 this enriched study design, the primary efficacy end-point was the change in spasticity Numerical Rating Scale (0–10 NRS) from the baseline to week 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. 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 anti-spasticity medications.

Methods
This was a 15-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 disturbances were assessed in this cohort 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 secondary and functional measures of spasticity, safety and tolerability, quality of life (QoL) and mood assessments were also collected throughout the study.

Inclusion and exclusion criteria
Inclusion criteria for this study were: 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 anxiety 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 optimum dose, based on efficacy and tolerability.
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 change in spasticity 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 per 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 nabiloximols compared with those randomized to placebo (data not shown). During Phase A, subjects had a mean daily number of 6.9 sprays (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 nabiloximols 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: 59.2%.
- 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: 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), which was statistically significant (P = 0.0002).

### Secondary endpoints

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 subjects (33%) on placebo. This approach statistically significant (P = 0.06).

Amoungst 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 = 0.0007), Physician Global Impression of Change (P = 0.005), Subject Global Impression of Change (P = 0.025) 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 4. Assessment of mood change using the Beck Depression Inventory.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nabiximols (mean)</th>
<th>Placebo (mean)</th>
<th>Treatment difference</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spasticity NRS</td>
<td>0.19</td>
<td>0.64</td>
<td>-0.45</td>
<td>0.0002</td>
</tr>
<tr>
<td>30% responder</td>
<td>0.74</td>
<td>0.51</td>
<td>-0.23</td>
<td>0.0003</td>
</tr>
<tr>
<td>50% responder</td>
<td>0.47</td>
<td>0.32</td>
<td>0.15</td>
<td>0.613</td>
</tr>
<tr>
<td>Spasm frequency</td>
<td>3.06</td>
<td>2.56</td>
<td>-0.50</td>
<td>0.005</td>
</tr>
<tr>
<td>Sleep disturbance NRS</td>
<td>-0.13</td>
<td>0.75</td>
<td>-1.88</td>
<td>0.0001</td>
</tr>
<tr>
<td>Modified Ashworth scale</td>
<td>0.68</td>
<td>1.63</td>
<td>-0.95</td>
<td>0.094</td>
</tr>
<tr>
<td>Morbidity index</td>
<td>-0.30</td>
<td>-1.20</td>
<td>0.90</td>
<td>0.630</td>
</tr>
<tr>
<td>Leg</td>
<td>-0.34</td>
<td>-0.21</td>
<td>0.13</td>
<td>0.439</td>
</tr>
<tr>
<td>Timed 10-m walk</td>
<td>-0.13</td>
<td>3.32</td>
<td>-3.46</td>
<td>0.009</td>
</tr>
<tr>
<td>EQ-5D Health state index</td>
<td>0.63</td>
<td>-0.05</td>
<td>0.68</td>
<td>0.002</td>
</tr>
<tr>
<td>EQ-5D Health state VAS</td>
<td>-1.99</td>
<td>-3.24</td>
<td>1.25</td>
<td>0.594</td>
</tr>
<tr>
<td>SF-36</td>
<td>0.30</td>
<td>0.76</td>
<td>-0.46</td>
<td>0.782</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>-0.31</td>
<td>0.98</td>
<td>-1.30</td>
<td>0.658</td>
</tr>
<tr>
<td>Role physical</td>
<td>-0.65</td>
<td>-0.50</td>
<td>0.15</td>
<td>0.060</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>-1.26</td>
<td>-0.12</td>
<td>1.14</td>
<td>0.442</td>
</tr>
<tr>
<td>Vitality</td>
<td>-1.17</td>
<td>-3.33</td>
<td>2.16</td>
<td>0.306</td>
</tr>
<tr>
<td>Social functioning</td>
<td>-0.97</td>
<td>-0.32</td>
<td>-0.65</td>
<td>0.840</td>
</tr>
<tr>
<td>Role emotional</td>
<td>-1.26</td>
<td>1.53</td>
<td>-2.79</td>
<td>0.343</td>
</tr>
<tr>
<td>Mental health</td>
<td>-2.20</td>
<td>-2.94</td>
<td>0.74</td>
<td>0.663</td>
</tr>
</tbody>
</table>

Safety and tolerability

All adverse events (AEs) experienced in subjects during both Phases A and B in the study are displayed in Table 5. 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 patients' 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 studies design only 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 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-
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, run-in period was single-blind. The response seen during the single-blind exposure period does not necessarily represent a response to Sativex. Rather, it 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. As it was only this subgroup of subjects blinded 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, none-the-less we believe that this design feature is likely to help maintain the blind to treatment allocation. Subject selection for 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 improved.

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 medication, or who find it intolerable, are unlikely to continue treatment for a prolonged period. Indeed, it is not desirable for such non-responding 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 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 had 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 1.8 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 patients 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 responsive 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.

Acknowledgements

This study was sponsored by GW Pharma Ltd.

Disclosure of conflict of interest

The authors confirm that there were no conflicts of interest in this study, A Novotna, J Mares, S Ratcliffe, I Novakova, M Vacha va, Zapletalova, C Gasperini, P Zannini, P. Rossi, Z. Ambler, Z. Stelmusiak, A. Erdmann, X. Montalban, A. Klimek, P Davies & the Sativex Spasticity Study Group were all investigators in this study and received investigator fees from GW Pharma Ltd. accordingly for their participation in the study.

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