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

Received 30 July 2010
Accepted 29 November 2010

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 produc-
tion of symptoms such as pain, spasticity, spasms and bladder dysfunction. Spasticity (stiffness) is a 
common and disabling symptom, 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 
both disability, 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, safe and effective treatments for 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 treat-
ment. 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 reflects normal 
clinical use, this study used an enriched enrolment 
design, in which only those participants who had 
achieved 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-tetrahydro- 
cannabinoid (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 spe-
cific cannabinoid receptors (CB1; CB2; CB receptors are 
preponderantly distributed in the CNS; CB2 receptors are 
located both in the CNS and extensively in the periphery (e.g., the immune system) [8]. Both of 
these 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 stim-
ulation and psychoactivity. CBD has anticonvulsant, 
muscle relaxant, anxiolytic, neuroprotective, antioxidant 
and antiinflammatory activity and has been shown to reduce 
the axiogenic and psychoactive effects of THC [8,10].

Nabiximols (Sanofi, GW Pharma Ltd, Salisbury, UK) contains THC + CBD at a nearly 1:1 fixed ratio and is 
described as an endocannabinoid system modula-

tor. It is derived from fully standardized chemotypes 
of Cannabis sativa L. plants developed to produce high 
and reproducible yields of the two principal cannabi-
noids (THC and CBD), with minor amounts of other 
cannabinoids and terpenes, prepared in a solvent 
containing ethanol, propylene glycol and corn 
meal oil for oral mucosal use through a sealed pump 
device.

Earlier studies using nabiximols showed a significant 
improvement in the patient-reported severity of spas-
ticity in patients with MS [11,12]. In addition, a meta-
analysis of three Sativex studies has demonstrated the 
efficacy of nabiximols in reducing spasticity measured 
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 pre-
liminary, single-blind, 4-week treatment period to iden-
tify 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 
average 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 is-
sues associated with the withdrawal of treatment.

The level of spasticity, spasm frequency and sleep 
disruptions was evaluated by a team of investigators 
and the change 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 tolerabil-
ity, quality of life (QoL) and mood assessments were 
also collected throughout the study.

A responder was defined as an improvement in this 
outcome measure 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 
withdraw from treatment.

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 sta-
ble dose for 6 months prior to and throughout the study.

Subjects had to have at least moderately severe 
spasticity, as defined by a score of 4 of 6 using a single 
spasticity Numerical Rating Scale (NRS) at screening. Each treating 
physician was asked to ensure that 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 initiated and no alterations to dosages 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 remain 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 disor-
der 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 can-
nabinoid-based medications in the 30-day period prior 
to study entry were excluded, as well as any subject with 
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 
oral mucosal 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 opti-
mal 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 Inven-
tory 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 dur-

ing 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

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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 (122 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 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: 58%;
- 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: -0.29 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 (P = 0.005). Subject Global Impression of Change (P = 0.0025) 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.

Figure 1 Disposition of subjects.
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 vitro 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 provide information about the average response to treatment, where those patients who fail to respond would not.

**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

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

<table>
<thead>
<tr>
<th>Gender</th>
<th>Male</th>
<th>Female</th>
<th>Ethnic origin</th>
<th>White/caucasian</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects (%)</td>
<td>120 (39)</td>
<td>96 (40)</td>
<td>5 (17)</td>
<td>330 (100)</td>
<td>241 (74)</td>
</tr>
</tbody>
</table>

| Age (years) (range) | 38.0 (16.4, 41.3) | 38.0 (17.4, 45.1) | 38.0 (17.4, 45.1) |

| BMI (kg/m²) (range) | 23.5 (17.4, 29.6) | 23.5 (17.4, 29.6) | 23.5 (17.4, 29.6) |

| EDSS score* (range) | 6.0 (1.8, 6.2) | 6.0 (1.9, 6.2) | 6.0 (1.9, 6.2) |

| Baseline spasticity (VAS) (range) | 6.0 (1.7, 7.0) | 6.0 (1.8, 7.0) | 6.0 (1.8, 7.0) |

| NRS (range) | 6.0 (2.0, 8.0) | 6.0 (2.0, 8.0) | 6.0 (2.0, 8.0) |

MS, multiple sclerosis, NRS, Numeric Rating Scale.

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

<table>
<thead>
<tr>
<th>Medication class/name</th>
<th>Sativex (% of)</th>
<th>Placebo (% of)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenosine derivatives</td>
<td>17 (15)</td>
<td>13 (15)</td>
<td>32 (15)</td>
</tr>
<tr>
<td>Benzodiazepine-receptor antagonists</td>
<td>21 (19)</td>
<td>25 (29)</td>
<td>45 (22)</td>
</tr>
<tr>
<td>Drotaverine</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>7 (7)</td>
<td>9 (10)</td>
<td>16 (8)</td>
</tr>
<tr>
<td>Griseofulvin</td>
<td>65 (63)</td>
<td>73 (62)</td>
<td>138 (65)</td>
</tr>
<tr>
<td>Tizanidine</td>
<td>20 (16)</td>
<td>20 (17)</td>
<td>40 (17)</td>
</tr>
<tr>
<td>Others</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>4 (2)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nabiximols (mean)</th>
<th>Placebo (mean)</th>
<th>Treatment difference (mean)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spasticity NRS</td>
<td>-1.05</td>
<td>0.64</td>
<td>-0.69</td>
<td>0.0002</td>
</tr>
<tr>
<td>30% responder</td>
<td>0.74</td>
<td>0.51</td>
<td>0.23</td>
<td>0.023</td>
</tr>
<tr>
<td>50% responder</td>
<td>0.41</td>
<td>0.32</td>
<td>0.09</td>
<td>0.003</td>
</tr>
<tr>
<td>Squat frequency</td>
<td>-0.30</td>
<td>0.26</td>
<td>-0.56</td>
<td>0.0005</td>
</tr>
<tr>
<td>Sleep disturbance NRS</td>
<td>-0.36</td>
<td>0.59</td>
<td>-0.95</td>
<td>0.0001</td>
</tr>
<tr>
<td>Modified Ashworth scale</td>
<td>0.08</td>
<td>0.13</td>
<td>-0.05</td>
<td>0.70</td>
</tr>
<tr>
<td>Morbidity index</td>
<td>0.09</td>
<td>0.08</td>
<td>-0.01</td>
<td>0.004</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>0.20</td>
<td>0.20</td>
<td>0.00</td>
<td>0.726</td>
</tr>
<tr>
<td>Role physical</td>
<td>-0.31</td>
<td>0.98</td>
<td>-1.29</td>
<td>0.03</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>-0.05</td>
<td>0.56</td>
<td>-0.61</td>
<td>0.088</td>
</tr>
<tr>
<td>General health</td>
<td>1.26</td>
<td>1.02</td>
<td>0.24</td>
<td>0.0002</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>-0.35</td>
<td>-0.32</td>
<td>0.03</td>
<td>0.30</td>
</tr>
<tr>
<td>Role emotional</td>
<td>-1.26</td>
<td>1.53</td>
<td>-2.79</td>
<td>0.04</td>
</tr>
<tr>
<td>Mental health</td>
<td>-2.20</td>
<td>-2.94</td>
<td>-0.74</td>
<td>0.683</td>
</tr>
</tbody>
</table>

95% confidence interval

<table>
<thead>
<tr>
<th>Lower</th>
<th>Upper</th>
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<tbody>
<tr>
<td>0.12</td>
<td>0.34</td>
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</tbody>
</table>

**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 (Phase B) (intention-to-treat analysis) | Nabiximols (mean) | Placebo (mean) | Treatment difference (mean) | P-value |
|-------|------------------|-----------------|-----------------|-----------------|---------|
| Spasticity NRS | -1.05 | 0.64 | -0.69 | 0.0002 |
| 30% responder | 0.74 | 0.51 | 0.23 | 0.023 |
| 50% responder | 0.41 | 0.32 | 0.09 | 0.003 |
| Squat frequency | -0.30 | 0.26 | -0.56 | 0.0005 |
| Sleep disturbance NRS | -0.36 | 0.59 | -0.95 | 0.0001 |
| Modified Ashworth scale | 0.08 | 0.13 | -0.05 | 0.70 |
| Morbidity index | 0.09 | 0.08 | -0.01 | 0.004 |
| Physical functioning | 0.20 | 0.20 | 0.00 | 0.726 |
| Role physical | -0.31 | 0.98 | -1.29 | 0.03 |
| Bodily pain | -0.05 | 0.56 | -0.61 | 0.088 |
| General health | 1.26 | 1.02 | 0.24 | 0.0002 |
| Vitality | -1.17 | -3.33 | 2.16 | 0.306 |
| Social functioning | -0.35 | -0.32 | 0.03 | 0.30 |
| Role emotional | -1.26 | 1.53 | -2.79 | 0.04 |
| Mental health | -2.20 | -2.94 | -0.74 | 0.683 |

95% confidence interval

<table>
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<td>0.12</td>
<td>0.34</td>
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</table>
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, the run-in period was single-blind. The response seen during the single-blind exposure period does not necessarily represent a response to Sativex, rather showed 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 with placebo, which could lead to subjects being left untreated during the initial 4 weeks of the study we 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 seem 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. Subject selection should be 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 [12].

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-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 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. Indeed, 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 estimated 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 in the spasticity NRS is 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 did withdraw from treatment early, eight were taking nabiloximols (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 conservative 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 nabiloximols.

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 nabiloximols 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 support to the subjective NRS measure of the primary end-point. The high degree of consistency between the NRS and secondary end-point scores (which are presented in the table) also supports the internal validity and re-assurance that the subjective NRS subject-rated assessment of efficacy of Sativex on the relief of spasticity is robust. The consistency of the Global Impres-