Synopsis

Clinical Report Synopsis for Protocol GWMS1137

Name of Sponsor:	**Name of Finished Product:**	**Name of Active Ingredient:**
GW Pharma Ltd	Sativex®	Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD)

Title of Study:

A multicentre, double-blind, randomised, parallel group, placebo-controlled study of the effect of long-term treatment with Sativex on cognitive function and mood of patients with spasticity due to multiple sclerosis.

Investigator(s) and Study Centres:

The Chief Investigator for this study was [redacted] n additional five centres in the Czech Republic took part in this study.

Publication(s) Reference:

Poster Presentation at the 29th Congress of the European Committee for Research and Treatment in Multiple Sclerosis and the 18th Annual Conference of Rehabilitation in MS in Copenhagen, Denmark, 2–5 October, 2013.

Study Period:	**Development Phase:**
Date of first signed informed consent: 12 Jan 2012 Date of last study observation: 13 May 2013	4

Objectives:

Primary Objective:

The aim of this study was to identify and further characterise the potential risks of memory loss and other psychological effects in patients with multiple sclerosis (MS). GW Pharma Ltd (GW) has already set up and initiated a non-interventional Sativex exposure Registry to address other risks and these two studies will form part of the post-marketing authorisation risk management commitment for Sativex.

This prospective cohort study was double-blind, randomised and placebo-controlled. In the study, parallel groups of patients with MS were randomised to receive either Sativex or placebo having met the study defined inclusion/exclusion criteria. Data from the two treatment groups on the parameters within Paced Auditory Serial Addition Test (PASAT) and Beck Depression Inventory-II (BDI-II) instruments was collected over a 48 week period and analysed.

The primary endpoint of the study was the change in cognitive function as assessed by the PASAT (combined PASAT I and II scores) total score from baseline (Visit 1) to end of treatment visit (Visit 5, Day 337) or withdrawal date.

Secondary Objectives:

- To evaluate the effect of Sativex on mood and spasticity.
- To assess the safety and tolerability of Sativex.

Methodology:

This was a 50-week multicentre, double-blind, randomised, placebo controlled, parallel group study to evaluate the effect of Sativex on cognitive performance in patients with spasticity due to MS. Following screening, eligible patients entered the study at the randomisation visit

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(Visit 1, Day 1). Further study visits took place at the end of 12 (Visit 2), 24 (Visit 3), and 36 weeks (Visit 4) of treatment, and at the end of the study (Week 48, Visit 5), or sooner if they withdrew. A safety follow-up visit took place 14 days after completion of the study or withdrawal (Week 50, Visit 6). At each scheduled clinic visit, patients were assessed for cognitive performance, mood, severity of spasticity, use of Investigational Medicinal Product (IMP), and the number of visits to a healthcare professional.

During the 48-week randomised treatment phase, patients self-administered their allocated randomised treatment on an outpatient basis, up to a maximum of 12 sprays to the oral mucosa per day (following an initial titration period).

Number of Patients (planned and analysed):

A total of 120 patients were planned, and 121 were randomised and analysed.

Diagnosis and Main Criteria for Inclusion:

Inclusion: Patients meeting the following criteria were considered eligible for this study:

- Patient aged 18 years or above.
- Diagnosed with any disease sub-type of MS.
- Diagnosed with symptomatic spasticity due to MS.
- Patient had at least moderate spasticity, in the opinion of the investigator.
- Patient fulfilled at least one of the two criteria below. Patient was either:
  - Established on a regular dose of anti-spasticity therapy, or
  - Had previously tried and failed anti-spasticity therapy.
- Stable medication regimen for at least four weeks prior to study entry, for all medications which could affect spasticity and/or cognition.
- If the patient was taking disease modifying medication, this had to be maintained at a stable dose for three months prior to the initial visit.
- Willing and able to give informed consent.
- Willing and able to comply with all study requirements.
- Willing for his or her name to be notified to the responsible authorities for participation in this study, as applicable.
- Willing to allow his or her primary care practitioner and consultant, if appropriate, to be notified of participation in the study.

Exclusion: The patient was not eligible for the study if ANY of the following applied:

- Any history or immediate family history of schizophrenia, other psychotic illness, severe personality disorder or other significant psychiatric disorder other than depression associated with their underlying condition.
- Any concomitant disease or disorder (such as poorly controlled epilepsy or seizures) that could influence the patient's level of cognition or mood.
- Currently using or had used cannabis or cannabinoid-based medications within 30 days of study entry and were unwilling to abstain for the duration of the study.
- Any known or suspected history of a diagnosed dependence disorder, current heavy alcohol consumption (more than 60 g of pure alcohol per day for men, and more than 40 g of pure alcohol per day for women), current use of an illicit drug, or current non-prescribed use of any prescription drug.

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- Any known or suspected hypersensitivity to cannabinoids or any of the excipients of the IMPs.
- Female patients of child bearing potential and male patients whose partner was of child bearing potential, unless willing to ensure that they or their partner used effective contraception during the study and for three months thereafter.
- Female patient who was pregnant, lactating or planning pregnancy during the course of the study and for three months thereafter.
- Patients who had received an IMP within the 12 weeks prior to the initial visit.
- Any other significant disease or disorder which, in the opinion of the investigator, could put the patient at risk because of participation in the study, could influence the result of the study, or could affect the patient's ability to participate in the study.
- Following a physical examination, the patient had any abnormalities that, in the opinion of the investigator, would prevent the patient from safe participation in the study.
- Patients previously randomised into this study.

Investigational Medicinal Product, Dose and Mode of Administration, Batch Number:

The treatment groups were:

1. Sativex

2. Placebo

The IMP consisted of one type of medication:

1. Sativex was presented as an oromucosal spray, containing an approximately 1:1 ratio of Δ-9-tetrahydrocannabinol (THC) (27 mg/mL):cannabidiol (CBD) (25 mg/mL) in ethanol:propylene glycol (50:50) excipients, with peppermint oil (0.05%) flavouring. The GW product code for Sativex is GW-1000-02.

Each actuation delivered 2.7 mg of THC and 2.5 mg of CBD.

Patient self-administered the IMP to the oral mucosa, except in those patients whose disabilities made this difficult, in which case a caregiver could administer the medication. Following an initial period of up-titration, the maximum dose within any 24 hour period was 12 sprays (THC 32.4 mg:CBD 30 mg).

Batch Number (BN) of IMP: K11026

Duration of Treatment:

Forty-eight week treatment period.

Reference Therapy, Dose and Mode of Administration, Batch Number:

Placebo was presented as an oromucosal spray, containing ethanol:propylene glycol (50:50) excipients, with peppermint oil (0.05%) flavouring and colourings FD&C Yellow No.5 (E102 tartrazine) (0.0260%), FD&C Yellow No.6 (E110 sunset yellow) (0.0038%), FD&C Red No. 40 (E129 Allura red AC) (0.00330%) and FD&C Blue No.1 (E133 Brilliant blue FCF) (0.00058%). The GW product code for placebo is GA-0034.

Each patient self-administered placebo to the oral mucosa, except in those patients whose disabilities made this difficult, in which case a caregiver could administer the medication. Following an initial period of up-titration, the maximum dose within any 24 hour period was 12 sprays.

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BN of placebo: K11024

Criteria for Evaluation:

Efficacy:

Primary efficacy endpoint: the change from baseline (Visit 1) to the end of treatment (Visit 5) in the PASAT total score (PASAT I and II scores combined).

Secondary efficacy endpoints: to evaluate the efficacy of Sativex compared with placebo on mood (as assessed by the BDI-II), timed 10-metre walk times, number of visits to a healthcare professional, Physician Global Impression of Change (PGIC), Subject Global Impression of Change (SCIG), Caregiver Global Impression of Change (CGIC) and Modified Ashworth Scale (MAS) scores.

Safety:

Assessments of the safety and tolerability of the IMPs was by volunteered adverse events (AEs), laboratory parameters, vital signs, physical examination and electrocardiogram. Treatment exposure and compliance were also measured by recording the mean, minimum and maximum daily number of sprays of IMP taken. Additionally, the incidence of suicidality, suicidal behaviour and suicidal ideation in the two treatment groups was summarised from the potential suicide events recorded on the Colombia-Suicide Severity Rating Scale (C-SSRS).

Statistical Methods:

The primary analyses of all efficacy endpoints used data from patients in the safety analysis set, which comprised all randomised patients who received at least one dose of IMP and had on-treatment efficacy data. Since a number of patients who withdrew from the study had their final clinic visit (Visit 5) carried out many days after IMP had been stopped, it was decided at the Blind Review Meeting (i.e. before the treatment allocation was unblinded) to exclude any clinic visit data (efficacy and also clinical laboratory results and vital signs) if they were recorded more than seven days after stopping treatment.

The primary analyses of change in PASAT total score from baseline (Visit 1) to the end of treatment (Visit 5) was analysed using analysis of covariance, with the baseline value as covariate and treatment group and centre as factors. From this analysis the adjusted treatment means, treatment difference, standard error and 95% confidence interval (CI) for the treatment difference were presented.

Sativex was deemed to be non-inferior to placebo (i.e. had no adverse effect on cognition) if the lower one-sided 97.5% confidence limit (CL) of the estimated treatment difference (Sativex-placebo) was greater than -10%.

A per protocol (PP) analysis set was also included for the analysis of the primary endpoint. Patients with compliance issues (negative urine THC results at the end of treatment [Sativex] or positive results [placebo]) were excluded from the PP analysis set (seven patients had urine THC results at the end of treatment (Visit 5) that were indicative of compliance issues).

The secondary efficacy endpoint of BDI-II was analysed using an approach analogous to the primary endpoint. Analysis of the other secondary endpoints (MAS, timed 10-metre walk and number of visits to a healthcare professional were also analysed using ANCOVA and appropriate non-parametric methods if the data were not found to be normally distributed. For the parameters of SGIC, CGIC and PGIC, data were summarised at all-time points and the final assessment at the end of treatment was analysed with ordinal logistic regression, using the proportional odds model with Global Impression of Change (GIC) as the dependent

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variable and treatment group as factor.

Summary - Conclusions:

Efficacy Results:

Primary endpoint (PASAT total score)

The mean PASAT total score increased (improved) from baseline to the end of treatment in both treatment groups. Adjusted mean increases from baseline to the end of treatment were +6.02 points from a baseline of 59.4 points for Sativex and +7.49 points from a baseline of 62.1 points for placebo, giving an estimated treatment difference of -1.47 points in favour of placebo. The lower one-sided 97.5% CL was -6.41 (greater than -10%) and so Sativex was deemed to be non-inferior to placebo in terms of its effect on cognition. The PP population results were similar, with an overall improvement in cognition in both treatment groups. Adjusted mean increases from baseline to the end of treatment were +5.90 points from a baseline of 61.0 points for Sativex and +7.47 points from a baseline of 62.2 points for placebo. Again, the lower one-sided 97.5% CL was -6.57 (greater than -10%).

Secondary endpoints

Mean BDI-II scores decreased (improved) from baseline to the end of treatment in both treatment groups. Adjusted mean decreases from baseline to the end of treatment were -2.84 points from a baseline of 15.7 points for Sativex and -2.55 points from a baseline of 13.5 points for placebo, giving an overall estimated treatment difference of -0.29 points that was in favour of Sativex treatment. The upper one-sided 97.5% CL was 2.33 points, which was less than 5% (3.15), therefore Sativex was deemed to be non-inferior to placebo in terms of its effect on mood. The reductions in scores took both group means from the 'mild depression' range (score between 14 and 19) to the 'minimal depression range' (score between 0 and 13) on the BDI-II scale.

MAS total scores decreased (improved) in both treatment groups from baseline to the end of treatment. Adjusted group mean decreases from baseline to the end of treatment were -10.41 points from a baseline of 38.1 points for Sativex and -8.05 points from a baseline of 35.9 points for placebo, giving an estimated treatment difference of -2.36 points that was in favour of Sativex treatment, but did not reach statistical significance (p=0.212, 95% CI: -6.09, 1.37 points).

Thirty patients (64%) in the Sativex group experienced some improvement in their 10-metre walk time from baseline to the end of treatment, compared with 24 (48%) taking placebo. However, this was non-significant (p=0.118).

The number of visits to a healthcare professional decreased (improved) from baseline to the end of treatment in both treatment groups. Although this difference favoured Sativex, the analysis of the data showed the presence of a treatment by centre interaction.

At the end of treatment, there were statistically significant improvements in all GIC outcomes in patients taking Sativex treatment compared with placebo (PGIC, p=0.002; SGIC, p=0.0001; CGIC, p=0.014). Overall, 71% of physicians (in the PGIC) reported an improvement (i.e. minimally better, much better or very much better) in the severity of the patient's spasticity since starting treatment in the Sativex treatment group compared to 40% in the placebo group. In the SGIC, 72% of patients taking Sativex reported an improvement in the severity of their spasticity since starting treatment compared to 38% taking placebo. Finally, 65% of carers (in the CGIC) reported an improvement in the severity of patient's spasticity since starting treatment in the Sativex treatment group compared to 40% in the placebo group.

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When the 'number of visits to a healthcare professional' data were tabulated by centre, improvements were seen in favour of Sativex for three centres and in favour of placebo in two centres. The remaining centre (276) showed no difference between treatment groups as its patients had no visits to a health care professional at any time during the study. Additional statistical analysis by non-parametric methods (Wilcoxon Rank Sum test) and by categorising the changes in the number of visits to a healthcare professional also failed to show a statistically significant difference between the two treatment groups (p=0.663 and p=0.620, respectively).

Safety Results:

The IMP was well tolerated in this study and the safety findings in longer term use over 12 months were considered unremarkable. No effects on depression or suicidality findings were identified. All causality treatment emergent AEs were reported in a total of 58 patients (47.9%) during the study. Thirty-nine (62.9%) patients in the Sativex group and 19 (32.2%) in the placebo group experienced AEs, with 25 (40.3%) and five (8.5%) patients in each respective group developing a treatment-related AE. Although there is a notable difference in the numbers of AEs reported between Sativex when compared to placebo, the frequency of AEs in the Sativex group matches closely to other clinical studies in patients with MS.

The most commonly reported treatment emergent all causality AEs occurred in the 'Nervous System Disorders' System Organ Class (SOC) with 20 (32.3%) patients randomised to Sativex and seven (11.9%) to placebo reporting at least one treatment emergent AE. The most common treatment emergent all causality AEs by Preferred Term were multiple sclerosis relapse and muscle spasticity, which were each experienced by seven patients overall (multiple sclerosis relapse in three [4.8%] patients randomised to Sativex and four [6.8%] patients randomised to placebo; muscle spasticity in five [8.1%] patients randomised to Sativex and two [3.4%] patients randomised to placebo).

Treatment-related AEs were also most commonly reported in the 'Nervous System Disorders' SOC; a total of 11 patients were affected, with 10 (16.1%) randomised to Sativex and one (1.7%) randomised to placebo. The most common treatment emergent treatment-related AEs by Preferred Term were vertigo (six [9.7%] patients randomised to Sativex) and fatigue (five [8.1%] patients randomised to Sativex and one [1.7%] to placebo). These were followed by dizziness in five (8.1%) patients, all randomised to Sativex. All other treatment-related AEs were experienced by only one or two patients each across the two treatment groups.

The majority of reported AEs were mild or moderate in severity with only eight AEs in five patients classified as severe. There were five patients who reported Serious Adverse Events (SAEs) during this study, all of which were taking Sativex. Only one patient developed SAEs that were considered to be treatment-related; these were disorientation, dysarthria and overdose, which were all mild in severity and resolved following interruption of the IMP.

There was one treatment emergent death during this study, caused by a severe AE of myocardial infarction in a patient randomised to receive Sativex, but that was not considered to be related to the study treatment.

A total of 11 patients (nine [14.5%] randomised to Sativex and two [3.4%] to placebo) experienced treatment emergent all causality AEs that led to their withdrawal from the study. Of these, six patients (9.7%) taking Sativex withdrew due to a treatment-related AE, compared with two patients (3.4%) on placebo. The two most common treatment-related AEs resulting in withdrawal were asthenia and dizziness (both experienced by two patients in the Sativex group), whilst all other events occurred in just one patient each. Those that were

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considered to be related to Sativex were single cases of vertigo, vomiting, application site discomfort, fatigue, weight decreased, decreased appetite, anxiety disorder due to a general medical condition and euphoric mood.

Laboratory sampling performed periodically through the study did not identify significant numbers of clinically significant changes, with no patterns emerging. In terms of vital signs, mean pulse rate, systolic and diastolic BPs remained consistent throughout the study and there was not deemed to be any notable patterns in patient's vital signs whilst on active treatment. In addition to the no observed change to mood findings from the BDI II, the findings from the C-SSRS also confirmed this result and did not identify safety concerns with regards to suicidality. Only three patients taking placebo had 'flags' indicative of certain ideations compared to one patient taking Sativex. At the screening visit (Visit 1), the patient randomised to Sativex had a 'flag' of 'wish to be dead' on the C-SSRS, due to unbearable pain; however, the patient did not express any suicidal behaviours. This event was not considered serious (in terms of scoring), was not treatment emergent, and there were no concerns at any subsequent visits.

In summary, the results of the safety analysis in this study do not raise any concerns with regards to the safety profile of Sativex.

Conclusion:

- There was a slight improvement in the PASAT total score from the beginning to the end of the study in both the Sativex and placebo groups, thus confirming that there is no evidence of long-term cognitive impairment in patients taking Sativex compared with those taking placebo. These findings are encouraging, especially given the patient population. The MS Trust website suggests that about half of all people with MS will have some degree of problem at some time with aspects of thinking such as memory, attention span or concentration.
- The change in mood (as measured by the BDI-II) over the 12 month period was more or less identical in the Sativex and the placebo group, confirming no untoward effect on mood.
- There was an improvement observed in spasticity on the MAS which did not reach statistical significance (possibly due to the fact that the current study was not powered to detect a statistically significant improvement in the MAS or due to well-documented issue of the MAS as a non-ideal measure of spasticity).
- There was a positive GIC profile (as assessed by caregivers, physicians and patients), the "gold standard" measure of a clinically significant improvement.
- Ten-metre walk times improved in more Sativex than placebo patients, as did the number of visits to a healthcare professional, indicating an improvement in condition, but this did not reach statistical significance.
- There was a good overall safety profile in this study, with no treatment-emergent suicidal tendencies in patients taking Sativex (as measured by the C-SSRS), a reassuring finding which was also reflected in the BDI-II results.

Date of the Report: 22 October 2013