Synopsis

Clinical Report Synopsis for Protocol GWSP0604

Name of Sponsor:	**Name of Finished Product:**	**Name of Active Ingredient:**
GW Pharma Ltd	GW-1000-02	Δ^9 tetrahydrocannabinol, 27 mg/ml: cannabidiol, 25 mg/ml, as extract of *Cannabis sativa* L

Title of Study:

A Two-phase, Phase 3 Study of the Safety and Efficacy of Sativex®, in the Symptomatic Relief of Spasticity in Subjects with Spasticity due to Multiple Sclerosis: Phase A - Single-blind Response Assessment; Phase B - Double-blind, Randomised, Placebo Controlled, Parallel Group Study.

Investigator(s) and Study Centres:

The Chief Investigator for the study was [redacted]

The study comprised a further 17 centres in the UK, 11 centres in Spain, 10 centres in Poland, eight centres in the Czech Republic and five centres in Italy.

Publication(s) Reference:

None to date.

Study Period:	**Development Phase:**
Date of first signed informed consent: 02 Jan 2008 Date of last study observation: 30 Jan 2009	3

Objectives:

Primary Objective:

To evaluate the efficacy of GW-1000-02 (named Sativex® in Canada and also named Sativex® oromucosal spray; United States Adopted Name (USAN): Nabiximols; WHO Anatomical Therapeutic Chemical (ATC) Code N02BG10) compared with placebo in relieving symptoms of spasticity due to multiple sclerosis (MS), in subjects identified as having a capacity to respond to GW-1000-02 (responders).

Secondary Objectives:

To evaluate the effect of GW-1000-02 compared with placebo on:

- Secondary measures of spasticity
- Functional measures of spasticity

Tertiary Objectives:

To evaluate the effect of GW-1000-02 compared with placebo on:

- Quality of life (QOL)
- Mood

Methodology:

This 19 week, multicentre study was conducted in two phases. Phase A was a preliminary, single-blind four week treatment period to identify subjects with a capacity to respond to GW-1000-02; eligible, consenting subjects entered a seven day screening period prior to returning to the study centre to begin a four week single-blind course of GW-1000-02 treatment. At the end of this phase, subjects' response to GW-1000-02 was assessed; those with the capacity to respond (i.e. at least a 20% reduction in mean 0-10 point numerical rating scale (NRS) spasticity score between screening and the end of the four week Phase A treatment) were eligible for entry into Phase B while those who did not respond took no further part in the study other than a follow up visit 14 days later.

Phase B was a 12 week double-blind, randomised, placebo controlled, parallel group study with visits at 28 day intervals and a final follow up visit 14 days after completion or withdrawal.

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The level of spasticity, spasm frequency and sleep disruption were collected each day during the entire study via an interactive voice response system (IVRS). In addition, study medication dosing data were recorded via IVRS throughout Phases A and B. Assessments of other secondary and functional measures of spasticity, safety and tolerability, QOL and mood were also gathered throughout the study.

Number of Subjects (planned and analysed):

The planned number of subjects was 488 in Phase A.

A total of 660 subjects were screened, of which 572 subjects entered the single-blind phase (Phase A) and received GW-1000-02. A total of 538 subjects completed Phase A of which 241 were then randomized into the double-blind phase (Phase B) (124 received GW-1000-02; 117 received placebo). A total of 224 subjects completed Phase B.

Diagnosis and Main Criteria for Inclusion:

Male or female subjects, 18 years or over and diagnosed with any disease sub-type of MS of at least six months duration and with at least moderate spasticity (defined by a score of ≥4 using a single spasticity severity NRS) of at least three months duration, which was not adequately relieved with current anti-spasticity therapy.

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

GW-1000-02: containing Δ^9 tetrahydrocannabinol (THC), 27 mg/ml: cannabidiol (CBD), 25 mg/ml, as extracts of *Cannabis sativa* L.

Subjects received study medication delivered in 100 µl actuations by a pump action oromucosal spray. Maximum permitted dose was 12 actuations (THC 32.4 mg:CBD 30 mg) in 24 hours.

Batch Numbers (BN): PGS30237, PGS30303, PGS30512 and PHS30024

Duration of Treatment:

Single-blind phase (Phase A)- four weeks; double-blind phase (Phase B) - 12 weeks

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

Placebo (GA0034): containing colourants and excipients.

Subjects received placebo delivered in 100 µl actuations by a pump action oromucosal spray. Maximum permitted dose was 12 actuations in 24 hours.

BN: PGS30236, PGS30304 and PGS30513.

Criteria for Evaluation:

Efficacy:

Primary Efficacy Endpoint: The difference in the effects of the two treatments on the change in mean spasticity NRS from baseline to the end of treatment.

Single-blind phase (Phase A): Changes in spasticity and sleep disruption NRS scores, spasm frequency as well as changes in Modified Ashworth Scale, Motricity Index, the timed 10 metre walk (in ambulatory subjects), Barthel Activities of Daily Living (ADL) Index, Carer, Physician and Subject Global Impression of Change (CGIC, PGIC, SGIC), EQ-5D questionnaire, SF-36 scores and mood assessment (Beck Depression Inventory-II).

Double-blind phase (Phase B): In addition to the Phase A efficacy endpoints, responder analyses at 30% and 50% levels were to be evaluated.

Safety:

In both parts: volunteered adverse events (AEs), laboratory parameters, vital signs and oral and physical examination.

Statistical Methods:

Single-blind phase (Phase A): No statistical hypothesis testing was performed, data were summarised at each time-point using descriptive statistics only. IVRS data were summarised using means over consecutive seven day intervals and during the last seven days on treatment.

Double-blind phase (Phase B): The primary analyses used the double-blind intention to

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treat (ITT) analysis set.
Statistical hypothesis testing was performed as appropriate. The null hypothesis was one of no difference between treatments. If the p-value for the comparison of treatments was less than 0.05 then the difference was deemed statistically significant and the null hypothesis rejected in favour of the alternative. As well as the p-value for each test of statistical significance, an appropriate estimate of the difference between the groups and its 95% confidence interval (CI) was presented.
The assumptions of normality and homogeneity of variance were checked where appropriate via examination of residual plots. In addition, normality was assessed using the Shapiro-Wilk test, based on the studentised residuals. For the primary and secondary analysis of covariance (ANCOVA) analyses of efficacy, studentised residuals that were larger than three were declared statistical outliers and their influence on the fitted model explored.

Summary - Conclusions:

Efficacy Results:
There were no notable differences in the demographics or baseline characteristics of the 331 subjects who were screened but were not randomised compared with the 241 subjects who entered the double-blind phase of the study. The demographics were similar between the two treatment groups in the double-blind phase of the study, with a mean duration of MS >12 years, spasticity >7 years. The subjects in the GW-1000-02 treatment group were slightly more severely disabled than those subjects in the placebo group, with a median Expanded Disability Status Scale (EDSS) of 6.5 and 6.0, respectively.
The primary efficacy endpoint of the spasticity NRS was highly statistically significantly in favour of GW-1000-02 treatment in comparison with placebo (p=0.0002). All secondary endpoints also showed a treatment difference in favour of GW-1000-02, with responders at the 30% level of response (p=0.0003), spasm frequency (p=0.005), sleep disruption NRS (p<0.0001), SGIC (p=0.023), CGIC (p=0.005), PGIC (p=0.005) and Barthel ADL index (p=0.007) being statistically significant. The treatment difference for the Modified Ashworth scale (p=0.094), timed 10 metre walk (p=0.069) and CGIC for ease of transfer (p=0.061) all approached statistical significance.
The change from the original screening baseline of the study by Week 4 in Phase A for the 241 subjects who entered Phase B was a mean improvement in spasticity of 3.01 points with GW-1000-02.

Safety Results:
The most prevalent treatment-emergent AEs in the single-blind phase (Phase A) were dizziness, (14%), fatigue (5.9%), somnolence (5.1%), dry mouth, (4.2%), nausea (4.0%) and vertigo (3.7%). The majority of AEs were rated mild to moderate in severity, with only 20 subjects (3.5%) experiencing severe events. One subject experienced a treatment-related SAE (muscular weakness, lethargy, mood altered and somnolence) but had confounding factors.
The most prevalent treatment-emergent AEs for GW-1000-02 in the double-blind phase (Phase B) were vertigo, (6%), dry mouth, (3%), somnolence (3%), and euphoric mood (3%). The majority of AEs were considered to be mild to moderate in severity, although there were twice as many severe AEs in the GW-1000-02 treatment group (6%) compared with the placebo group. Only one subject, in the GW-1000-02 group, experienced a treatment-related serious adverse event (SAE) (suicidal ideation). There were two deaths, both in the GW-1000-02 treatment group. One subject succumbed to urosepsis, the other to bronchopneumonia. Neither event was considered to be treatment-related. A total of nine subjects (7%), all in the GW-1000-02 group, stopped study medication due to AEs. Approximately half of the AEs leading to permanent cessation of study medication were considered to be treatment-related and there was no pattern evident in their distribution.

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There were no differences in changes in mood between the groups, as assessed by the Beck Depression Inventory-II (BDI-II). No suicidal ideation differences were seen between GW-1000-02 and placebo.

Conclusion:

- The results from this study support the proposal that GW-1000-02 is effective and well tolerated in the treatment of subjects who are suffering from refractory spasticity due to MS, using a study methodology specifically recommended by UK and other European regulatory agencies. The primary endpoint of the study (i.e., the adjusted mean difference in NRS score between GW-1000-02 and placebo) was -0.84 points in favour of GW-1000-02. This treatment difference was highly statistically significant (p=0.0002).
- The positive outcome of the primary efficacy measure was supported by secondary outcome measures and the findings from functional assessments. The presence of unequivocal functional improvement is confirmed by the observation that the improvement in subject reported spasticity is supported by conventional means of assessing function such as timed 10 metre walk, the carer and physician global impression of function and the Barthel ADL Index.
- The study has demonstrated that non-responders to GW-1000-02 can be identified by means of a short therapeutic trial (i.e., no more than four weeks), thereby avoiding exposure to ineffective treatment for a prolonged period.
- The clinical significance threshold (i.e., 30% improvement at the end of the study versus baseline) in the subjects who were identified as being responders after the four week trial period was statistically significantly higher in the group of subjects receiving GW-1000-02 compared with the placebo group (p= 0.0003)
- In the setting of a therapeutic trial, the AE profile after the first four weeks on active medication is essentially similar to that of placebo.
- There was no evidence of a withdrawal syndrome in those subjects who stopped GW-1000-02 abruptly at the end of the study after 16 weeks on the medicine.
- The improved safety profile, in comparison with earlier clinical trials of GW-1000-02, is likely to have resulted from the modified, more conservative dose titration regimen employed in the study. Approximately half of GW-1000-02 exposed subjects reported no AEs. The other half experienced mostly mild to moderate transient AEs. The withdrawals secondary to tolerability/safety issues were low.

Date of the Report: 17 April 2009