Synopsis

Clinical Report Synopsis for Protocol GWSP0702

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

Title of Study:

A placebo controlled, parallel group, randomised withdrawal study of subjects with symptoms of spasticity due to multiple sclerosis who are receiving long-term GW-1000-02 (Sativex®).

Investigator(s) and Study Centres:

The chief investigator for the study was [redacted]

The study comprised a further four centres in the UK.

Publication(s) Reference:

None to date.

Study Period:	**Development Phase:**
Date of first signed informed consent: 12 Nov 2007 Date of last study observation: 16 Jan 2009	

Objectives:

Primary Objective:

To evaluate the maintenance of effect of GW-100-02 [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 spasticity due to multiple sclerosis (MS), in subjects who had been receiving long-term benefit from GW-1000-02.

Secondary Objectives:

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

- Secondary measures of spasticity
- Functional measures of spasticity
- Sleep quality (disruption)

To assess the safety and tolerability of GW-1000-02 withdrawal.

Methodology:

This five week (one week baseline and four weeks randomised treatment period), multi-centre, placebo controlled, parallel group, randomised withdrawal study was designed to evaluate the maintenance of effect after long-term treatment with GW-1000-02 in subjects with symptoms of spasticity due to MS who had been receiving long-term benefit from treatment with GW-1000-02. Subjects were selected from the Supply of Unlicensed Sativex (GW-1000-02) (SUS) or named patient supply programmes and had been receiving Sativex for at least 12 weeks prior to study entry. Following informed consent and screening, eligible subjects entered the study (Visit 1, Day B1) and commenced a seven day open label baseline period. They then returned for a randomisation visit (Visit 2, Day 1), at which point they were randomised to receive either GW-1000-02 or placebo (randomised withdrawal period). Subjects returned to the centre for an end of study visit at Week 5 (Visit 3, Day 28) or earlier if they withdrew from treatment. Spasticity and sleep disruption review and dosing diaries

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were completed each day from the start of the baseline period until completion or withdrawal.

Number of Subjects (planned and analysed):

No formal sample size calculation was performed, however it was estimated that approximately 60 subjects (30 per group) would be randomised into the study. A sufficient number of subjects were to be screened to achieve this target.

In total 36 subjects were recruited and analysed (18 received GW-1000-02; 18 received placebo). A total of 17 subjects completed the study (GW-1000-02, 15; placebo, two).

Diagnosis and Main Criteria for Inclusion:

Male or female subjects aged 18 years or over, taking a minimum of two sprays per day of GW-1000-02 for the relief of their spasticity due to MS, for at least 12 weeks prior to study entry.

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. Subjects administered study medication at the same tolerated dosage of GW-1000-02 that they used prior to study participation. This could be up to a maximum permitted dose of eight actuations in any three hour period and 48 actuations (THC 130 mg:CBD 120 mg) in 24 hours.

Batch Numbers (BN): PGS30237, PHS30024

Duration of Treatment:

Five 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. Subjects administered study medication at the same tolerated dosage of GW-1000-02 that they used prior to study participation. This could be up to a maximum permitted dose of eight actuations in any three hour period and 48 actuations in 24 hours.

BN: PFS30944, PGS30513, PHS30239

Criteria for Evaluation:

Efficacy:

Time to treatment failure in the randomised withdrawal period, changes in spasticity severity and daily sleep disruption 0-10 numerical rating scales (NRS), Modified Ashworth Scale, Timed 10-metre walk, Motricity index and carer and subject global impressions of change (CGIC and SGIC).

Safety:

Volunteered adverse events (AEs), laboratory parameters, vital signs and oral examination.

Statistical Methods:

Data was summarised using descriptive statistics and statistical models were fitted to the data as appropriate. From these models, predicted treatment differences were presented along with

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appropriate confidence intervals.

The primary endpoint of the time to treatment failure in the randomised-withdrawal phase was summarised and analysed using the withdrawal analysis set. This was analysed using Kaplan-Meier survival analysis methodology and proportional odds modelling, with randomised-withdrawal treatment as a factor.

For the secondary endpoints of the change in spasticity severity NRS, sleep disruption NRS, Modified Ashworth Scale, Motricity Index and Timed 10 metre walk from baseline to end of study was analysed using a linear model. Both the Subject Global Impression of Change (SGIC) and Carer Global Impression of Change (CGIC) were analysed with ordinal logistic regression using the cumulative proportional odds model.

Summary - Conclusions:

Efficacy Results:

The demographics were similar between the two groups, with a mean duration of MS >16 years, spasticity >12 years and EDSS of 7.0.

A total of 94% of subjects on placebo failed treatment compared with 44% of subjects from the GW-1000-02 group. The difference in time to treatment failure was statistically significant in favour of GW-1000-02 (p=0.013). The reason for failure in the majority of subjects (76%) was a worsening of spasticity i.e. ≥ 20% increase in NRS score from baseline. With the exception of the Modified Ashworth Scale all other secondary endpoints showed a treatment difference in favour of GW-1000-02, with the SGIC ((p=0.017) and carer functional-ability global impression of change (p=0.001) being statistically significant.

Safety Results:

No new safety issues were raised as a result of this study.

During the seven day open-label baseline period, one subject (6%) reported a treatment-related AE of nausea. During the randomised withdrawal phase nine subjects (50%) receiving GW-1000-02 and 10 subjects (56%) receiving placebo experienced a treatment-related AE. .The most prevalent treatment-related AEs in the GW-1000-02 subjects were fatigue (two subjects, 11%), pain (two subjects, 11%), muscle spasticity (two subjects, 11%) and spasms (two subjects, 11%). A total of two subjects (11%) receiving GW-1000-02 and nine (50%) subjects receiving placebo ceased treatment due to AEs during the randomised withdrawal phase. Only one subject experienced SAEs; arthralgia and pain in extremity during the study and lumbar spinal stenosis diagnosed post-study. The events were considered to be not related to the study medication.

Biochemistry, haematology and urinalysis parameters showed no notable trends and no effect on vital signs or oral abnormalities on examination were evident; no clinically significant findings were observed.

Conclusion:

- The results from this study support the proposal that the efficacy of GW-1000-02 is maintained in long-term use for subjects suffering from spasticity due to MS, using a study methodology specifically recommended by UK and European regulatory agencies.
- These findings in this randomised withdrawal study add support to previously published open-label studies of GW-1000-02.
- There was no evidence of a withdrawal syndrome in those subjects who stopped GW-1000-02, despite a prolonged period on the medicine.

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Date of the Report: 16 April 2009		