Synopsis

Clinical Report Synopsis for Protocol GWCA0701

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

Title of Study:

A double blind, randomized, placebo controlled, parallel group dose-range exploration study of Sativex® in relieving pain in patients with advanced cancer, who experience inadequate analgesia during optimized chronic opioid therapy

Investigator(s) and Study Centers:

The Chief Investigator for the study was [redacted].

The study comprised a further 23 centers in the USA, 14 centers in Romania, 12 centers in the Czech Republic, nine centers in both the UK and South Africa, seven centers in Spain, five centers in Poland, four centers in Chile, three centers in Canada and Italy, two centers in Mexico, one center in Belgium, Finland and Germany.

Publication(s) Reference:

None to date.

Study Period:	**Development Phase:**
Date of first signed informed consent: 16 Nov 2007 Date of last study observation: 9 Jan 2010	2b

Objectives:

Primary Objective:

The primary objective was to determine the effective dose range and to demonstrate a non-effective dose range of Sativex (named Sativex® in Canada and also named Sativex® oromucosal spray; United States Adopted Name [USAN]: Nabiximols; WHO Anatomical Therapeutic Chemical [ATC] Code N02BG10) in patients who had advanced cancer, who were experiencing inadequate analgesia during optimized chronic opioid therapy.

Secondary Objectives:

To evaluate the efficacy of Sativex compared with placebo on:

- Secondary measures of pain relief
- Sleep disruption
- Patient Assessment of Constipation Quality of Life (PAC-QoL)
- Patient Global Impression of Change (PGIC)
- Montgomery Asberg Depression Rating Scale (MADRS)
- Addiction Research Center Inventory (ARCI)

To assess the safety and tolerability of Sativex.

Tertiary Objectives:

To evaluate the effect of Sativex compared with placebo on:

- Quality of Life
- The opioid composite assessment (numerical rating scale (NRS), versus fixed dose opioid consumption)

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- Consumption of opioid.

Methodology:

This was a nine week (five to 14 day baseline, five week treatment period, including a one week titration period, followed by a two week follow up visit), dose ranging study. Eligible patients entered the study (Visit 1, Day B1) and commenced a baseline period. Pain (average pain and worst pain) and sleep disruption scores, and opioid usage were collected using an Interactive Voice Response System (IVRS) each day during the baseline period and in addition, study medication usage was also collected via IVRS during the treatment period. In order for the patient to be eligible for randomization, their level of pain and opioid consumption must have met the eligibility criteria. During the baseline period the mean of the average pain scores must have been ≥4 and ≤8 on an 11-point NRS for three consecutive days. Patients then returned for a randomization visit (Visit 2, Day 1) and were randomized into one of three cohorts – a low dose cohort (1-4 sprays per day), medium dose cohort (6-10 sprays per day), and high dose cohort (11-16 sprays per day). The patients in each cohort received either Sativex or placebo using a 3:1 allocation ratio. Patients titrated up into their target dose range during Week 1 and were then required to maintain a stable dose for the remainder of the study, where possible. A further visit took place at the end of Week three (Visit 3 Day 22). Patients returned to the center for an end of treatment visit at Week five (Visit 4, Day 36) or earlier if they prematurely terminated from the study. A post-study follow up telephone call (Visit 5) occurred 14 days after Visit 4 or after premature termination.

Number of Patients (planned and analyzed):

The planned number of patients was 336 (112 in each dose cohort [84 Sativex and 28 placebo].

In fact, a total of 503 patients were screened (30 of whom had been re-screened), of which 360 patients were randomized (269 to Sativex [91 to the low dose group, 88 to the medium dose group, 90 to the high dose group] and 91 to placebo). A total of 263 patients completed the study (of which 197 received Sativex [71 in Sativex low dose group, 67 in Sativex medium dose group, 59 in Sativex high dose group]; 66 received placebo).

Diagnosis and Main Criteria for Inclusion:

The patient population was one with advanced active cancer, which was incurable and who had been defined both in the opinion of the investigator, and according to agreed criteria, to still have moderate to severe pain despite maximum tolerated doses of morphine or morphine equivalents. In particular, the study entry criteria excluded those patients in whom the investigator believed that a change of opioid medication, either of route of administration, or of agent, would be likely to bring additional relief at no greater risk. In this way, the study was aiming to address a population with a clearly identified and genuine medical need.

The identification of the patient population as described in the Inclusion and Exclusion Criteria made it clear that the Investigational Medicinal Product (IMP) was to be used only in those patients who were deemed to be unlikely to achieve additional pain relief by simply increasing their daily opioid dose or where the patient was currently, or had previously experienced intolerable side effects caused by the opioid analgesia, and which had prevented the patient from increasing the maintenance dose of opioid therapy any further. These were by definition patients with advanced cancer who had no curative treatment options.

In order to be eligible for enrollment, patients were 18 years or over and must have had advanced active cancer, of any type, which was considered incurable. Patients must have

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been receiving a sustained release (SR) fixed dose of opioid therapy (excluding Methadone) at the time of entry to the study. In order to be eligible for randomization, the average pain scores must have been ≥4 and ≤8 during the baseline period which did not change by more than two points on the 11-point NRS for three consecutive days.

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

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

Patients received study medication delivered in 100 µl actuations (THC 2.7 mg:CBD 2.5 mg) by a pump action oromucosal spray. Maximum permitted dose was four, 10 and 16 actuations for the low, medium and high dose cohorts, respectively, in 24 hours, administered in a twice daily dosing regimen.

Batch Numbers (BN) of IMP: PHS30329, PHS30026, PGS30303, PGS30512 PFS30773, PHS30332 and PHS30024.

Duration of Treatment:

Five week treatment period.

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

Placebo (GA0034): containing colorants and excipients.

Patients received placebo delivered in 100 µl actuations by a pump action oromucosal spray. Maximum permitted dose was four, 10 and 16 actuations for the low, medium and high dose cohorts, respectively, in 24 hours, administered in a twice daily dosing regimen.

BNs: PHS30331, PHS30239, PGS30304, PGS30513 and PFS30944.

Criteria for Evaluation:

Efficacy:

The primary efficacy endpoint: the patient 30% pain response status, where a response was defined as a 30% or greater reduction in the NRS score (average pain) during the last three days of Week 5 compared with the three day baseline period.

The secondary efficacy endpoints: evaluated the effect of Sativex compared with placebo on: the percent improvement in pain across the spectrum of response levels (i.e., the continuous response analysis); mean daily IVRS NRS pain score (average pain); mean daily IVRS NRS pain score (worst pain); repeated measures analysis (average pain); Brief Pain Inventory-Short Form (BPI-SF); sleep disruption NRS; PAC-QoL; PGIC; MADRS; ARCI. Sensitivity analyses were performed on the main efficacy endpoints to assess the effects of any changes in opioid medications.

The tertiary efficacy endpoints: proportion of patients showing a response from baseline to the end of Week five using the opioid composite assessment (change in average pain NRS versus change in opioid fixed dose consumption); opioid fixed dose consumption and the episodes of breakthrough analgesia taken and quality of life measures (i.e., The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30.

Safety:

Assessments of the safety and tolerability of Sativex by volunteered adverse events (AEs), laboratory parameters, vital signs and oral and physical examination.

Statistical Methods:

The primary analyses of all efficacy endpoints used the data for patients from the intention-to-treat (ITT) analysis set.

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The primary efficacy endpoint was the patient 30% pain response status during the last three days of Week 5. A positive 30% pain response was defined as a reduction of at least 30% in the mean 11-point NRS pain score (average pain intensity) from baseline to the last three days of Week 5. Patients who withdrew from the study before Week 5 were considered to have not responded unless withdrawal was due to disease progression or death, in which cases their last weeks' average pain scores were used to determine response status.

The proportions of responders were compared between the treatments using logistic regression with region (North America/Rest of the World) and treatment used as factors. The primary comparisons of interest were each of three active treatments versus placebo. The assumption that the response in the placebo groups for the three dose cohorts was similar was tested before pooling the data in the analysis of efficacy.

The analysis of all secondary efficacy assessments was considered supportive and no formal adjustments for multiple comparisons were made.

The cumulative response to treatment was shown by plotting cumulative response rates against increasing thresholds for response, i.e. percentage changes from baseline in the mean 11-point NRS pain score which defined a response. The cumulative response curves were compared between the treatments appropriately.

The PGIC was analyzed with ordinal logistic regression using the proportional odds model with baseline mean pain as a covariate and region and treatment as factors.

The change from baseline to the end of treatment for all other secondary endpoints was analyzed using analysis of covariance (ANCOVA) with baseline value as a covariate and region and treatment as factors.

The patient data was tabulated using summary statistics as appropriate. An analysis was performed to assess pain in subgroups of patients with different consumption levels of pain maintenance medication at baseline

Analyses of the primary endpoint were also performed for the per-protocol (PP) analysis set, which investigated the effect of mean dose received during the primary endpoint assessment period, rather than randomized treatment.

The tertiary endpoints were analyzed using similar approaches to the secondary endpoints.

All safety data collected was listed and summarized appropriately.

Summary - Conclusions:

Efficacy Results:

A total of 360 patients were randomized. The demographics were similar between the treatment groups, with an overall mean duration of cancer of 3.6 years and a baseline pain score of 5.8 on the NRS. At baseline, the median daily dose of maintenance opioid background medication in the whole study population was 120 mg of oral morphine equivalents.

The results of the 30% responder rate analysis, were numerically in favor of the Sativex low and medium dose groups but did not show a statistical difference from placebo (n=30 [33%] vs. n=24 [26%], p = 0.33; n=26 [30%] vs. n=24 [26%], p = 0.61, respectively). The high dose Sativex group was inferior to placebo. Sativex demonstrated a significant improvement in the percent improvement in pain across the spectrum of response levels (i.e., the continuous response analysis) as compared to placebo for all doses of Sativex (p=0.035), for the low dose and mid dose groups (treatment difference of -12.5%, p = 0.008; median treatment difference -8.75%, p=0.039, respectively), but not for the high dose group (p=0.675).). For the mean change from baseline in pain NRS, the results indicated an overall treatment difference

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(p=0.027) and this difference was most marked in the low dose group (treatment difference of -0.75 points, p=0.006). The secondary analysis of worst pain was consistent with the primary findings; marked treatment difference in in favor of Sativex for the low dose group (treatment difference of -0.73 points, p=0.011).

There was an improvement in sleep disturbance, indicating an overall treatment difference (p=0.012) which was statistically significant for Sativex low dose group (treatment difference of 0.88 points, p=0.003). There were no notable treatment differences observed with the BPI-SF, the PGIC, the PAQ-QOL or the MADRS. The opioid composite score approached significance for the Sativex treated patients overall (p=0.077), and was significant for the low dose group (p=0.038). A series of analyses combining results for the low and medium dose groups suggest that the optimum dose range for Sativex is from three or four up to 10 sprays per day.

Safety Results:

Patients in the high Sativex dose group did not tolerate the study medication well with 28% of them discontinuing the study due to AEs. Also, 33.7% patients in the high dose group took their medication below their target dose at the end of the treatment period. It is also important to note that an analysis of the low dose (1-4 sprays) group shows that over 90% of patients titrated to a dose of 3 or 4 sprays per day.

There appeared to be a relationship between the dose of Sativex and the incidence of treatment-emergent AEs, with a higher number of patients reporting treatment-emergent AEs in the high dose group (91.1%) compared to the other two Sativex treatment groups (low dose 74.7% and medium dose 83.9%) and placebo (75.8%); this was in turn reflected in the number of patients who discontinued study medication due to AEs (Sativex high dose group 27.8% compared to Sativex low dose group, 14.3%, Sativex medium dose group, 17.2% and placebo, 17.6%). The most common treatment-related AEs developed by patients in the different treatment groups were dizziness (combined Sativex = 16.8% compared to placebo = 9.9%), somnolence (combined Sativex = 12.3% compared to placebo = 4.4%) and nausea (combined Sativex = 11.2% compared to placebo = 7.7%). There were no treatment related deaths during this study. There were no consistent abnormalities observed in the laboratory results.

In describing and analyzing the SAEs, consideration must be given to the fact that the patient population in this study was one with advanced cancer, who were receiving in most cases multiple medications, had experienced several lines of anti-cancer treatment, and had a limited life expectancy. A total of 30.2% of the Sativex treated patients experienced an SAE compared with 25.3% of the placebo group. Overall, 20.9% of all patients randomized to receive Sativex died during the course of the GWCA0701 study (including data up to 28 days after final dose) compared with 17.6% of placebo patients. This overall death rate is reflective of a population of patients with advanced cancer. The number of deaths in the low dose Sativex group was higher than that in the other groups.

Conclusion:

Sativex provided efficacy as shown above, maximally in the low and medium dose groups. These doses were apparently consistently more effective across all parameters, than the high dose group. Sativex was well tolerated in the low and medium dose groups as well.

The high dose group (11-16 sprays per day) did not demonstrate analgesic efficacy – treatment was also poorly tolerated in this dose group. A total of 25 of 90 (28%) patients in the high dose group experienced AEs that led to withdrawal from treatment. In contrast, the rate of AEs leading to withdrawal in the low and medium dose groups was comparable to

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placebo. Also, of the 90 patients randomized to the high dose group, only 57 (63%) remained in the dose group at the end of the study – the remainder having been unable to continue taking the required dose. With regards to risk, it is apparent that these data suggest that doses of 11 sprays or higher are reaching a maximum tolerated dose without any advantage of improved efficacy. Thus it can be concluded that doses of 11 sprays and above are unlikely to provide a satisfactory risk/ benefit profile except in a few individuals. On the contrary, the low and medium dose groups were associated with a lower or similar rate of AEs to placebo, and a low rate of withdrawal from the study due to AEs. On the benefit side, efficacy was observed in both the low and medium dose groups, reaching statistical significance for the continuous response analysis and for the mean change from baseline for those patients in the low group and for the continuous response analysis for patients in the mid dose group. When results from these two dose groups were combined, Sativex was superior to placebo for the mean change from baseline and for the continuous response analysis, as well as for the important secondary efficacy measure of sleep quality.

It can therefore be concluded that the range of doses of three to 10 sprays shows a favorable risk/benefit profile, and that an appropriate approach to dosing in the proposed Phase 3 studies is to permit within patient dose titration to within the dose range of 3 to 10 sprays per day. Daily doses of 11 sprays and above are unlikely to provide a satisfactory risk/benefit profile and therefore should not be taken forward into Phase 3. These results are consistent with those seen in the earlier European study, GWCA0101 where the median daily dose taken by the Sativex treatment group was 8.15 sprays per day.

Date of the Report: 29 Nov 2010