

## Objective

This presentation reports results of Phase III clinical trials and safety extension studies (SAFEX) on the effects of Sativex® (GW-1000-02), a cannabis based medicine (CBM) produced by GW Pharmaceuticals, on sleep in the context of medical treatment of neuropathic pain (NP), spasticity, lower urinary tract symptoms (LUTS), and other manifestations of multiple sclerosis (MS).



Figure 1: Sativex® cannabis based medicine (CBM) in pump-action spray.

## Background

Sativex® (Fig. 1) is a highly standardized medicinal product composed of liquid carbon dioxide extracts from selected strains of cloned *Cannabis sativa* plants grown under conditions of Good Agricultural Practice (GAP), to produce high and reproducible yields of the principle active cannabinoids,  $\Delta^9$ -tetrahydrocannabinol (THC) and cannabidiol (CBD). Sativex is combination of extracts from two clonal cannabis cultivars, a high THC extract (Tetranabinex®) and a high CBD extract (Nabidolex®). The dried inflorescences of unfertilized female cannabis plants are extracted and refined under current Good Manufacturing Practice (GMP) conditions to yield a botanical drug substance (BDS) of defined composition. The contents of the principle actives in the BDS are well controlled and reproducible from batch to batch, and represent some 70% (w/w) of the total BDS (1). Minor cannabinoids are present (5 – 6%). The remainder of the BDS consists of terpenes (6 – 7%, most GRAS (Generally Recognized as Safe)), steroids (6%), triglycerides, alkalanes, squalene, tocopherol, carotenoids and other minor components (also GRAS) derived from the plant material (2). The most significant cannabinoid and non-cannabinoid components are controlled within the BDS specification. BDS is formulated into a spray for sub-lingual and oral-pharyngeal administration. Each 100  $\mu$ L pump-action spray contains 2.7mg of THC and 2.5mg of CBD, the minor components, plus ethyl alcohol; propylene glycol excipients. Detailed pharmacokinetic data on this material is available (3). The preparation has onset of activity in 15-40 minutes, which allows patients to titrate dosing requirements according to symptoms, with a very acceptable profile of adverse events. A total of 800 patient years of Sativex exposure in over 1400 experimental subjects has been amassed in Phase II-III clinical trials. A majority of subjects have had no previous recreational or medicinal cannabis exposure. Data from a total of approximately 323 subjects with multiple sclerosis and approximately 200 subjects with neuropathic pain were examined for the purposes of this study.

## Design/Methods

Patients were studied employing CBM in self-titrated doses in randomized placebo controlled double-blind clinical trials. In each instance, CBM was added to existing medication regimens in patients whose symptoms of pain, spasticity, etc., remained intractable. Thus, any observed benefit was above and beyond previously attained treatment benchmarks. Additional SAFEX studies provided data on long-term effects in the 75% of patients who wished to continue the study drug with monitoring of daily dosages and symptoms.

After initial Phase I studies, improvements in sleep quality in clinical trials were based on patients' subjective assessments, such as number of waking episodes.

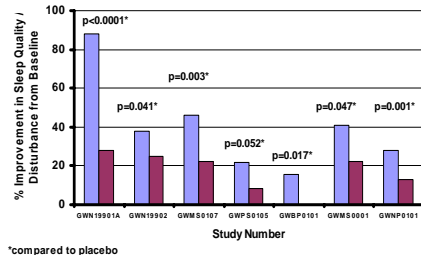
## Results

In a Phase I study of eight normal subjects with electroencephalographic monitoring, Sativex produced less sedation than a THC-predominant extract, demonstrated some alerting properties during sleep, and reduced residual sedative effects of THC the following day (4). While THC 15 mg extract alone produced little effect on sleep architecture, sleep latency was reduced, memory was impaired, and residual sleepiness and mood changes were observed ( $p < 0.05$ ). Both dose levels of Sativex decreased Stage 3 sleep ( $p < 0.05$ ) over placebo, and the 15 mg doses increased wakefulness ( $p < 0.05$ ) compared to 5 mg doses. The 5 mg doses of Sativex actually produced faster reaction times on the digit recall test ( $p < 0.05$ ) over placebo. Although impaired memory was observed the next day when 15 mg THC extract was administered, no effects on memory were observed when 15 mg THC was co-administered with 15 mg CBD as Sativex. It was felt that the THC: CBD combination produced therapeutic advantages over effects seen with single components, as CBD counteracted residual effects of THC on daytime sleep latencies and memory. Conclusions were that THC was sedative, while in contrast the presence of CBD was alerting, and tended to counteract THC residual effects.

In previously published Phase II clinical trials, Sativex significantly improved sleep quality in 20 patients with intractable neurogenic symptoms ( $p < 0.05$ ) (Study GWN19902) (Fig. 2)(5), while 34 patients with intractable NP demonstrated a surprising conversion of subjective sleep from poor or fair to good quality ( $p < 0.0001$ ), and sleep duration ( $p < 0.0001$ ) (Study GWN1991A) (Fig. 2)(6). Patients with intractable lower urinary tract symptoms (LUTS) due to MS also showed significant improvement in sleep self-assessment ( $p < 0.05$ ) (7).

In a Phase III randomized placebo controlled clinical trial in central neuropathic pain due to MS over 5 weeks in 66 patients, significant benefit of Sativex over placebo was observed in sleep disturbance ( $p = 0.003$ ) (Study GWMS0107)(8)(Fig. 2). A Phase III trial in intractable pain in 79 subjects (Study GWPS0105) also showed a strong trend toward benefit on sleep ( $p = 0.045$ ) (Fig. 2). In a Phase III randomized placebo controlled study of 63 Sativex subjects with peripheral neuropathic pain characterized by allodynia produced more marked reductions in sleep disturbance ( $p < 0.001$ ) (Study GWNP0101)(9)( Fig. 2). In the largest clinical study of brachial plexus avulsion and central neuropathic pain to date (10)(Study GWBP0101) in 48 subjects in a double-blind crossover design of placebo vs. oromucosal THC CBM (Tetranabinex®) vs. Sativex, sleep parameters diverged from a baseline of 4.8 to 5.2 with placebo (NS), to 6.0 with Tetranabinex ( $p < 0.001$ ) and 5.9 with Sativex ( $p < 0.01$ ) (Fig. 2).

Summary of Impact of Sativex on Sleep Quality / Disturbance



\*compared to placebo

Figure 2: Sativex effects on sleep in Phase II-III clinical trials of NP and MS.

Another Phase III study of various symptoms in MS (11)(Study GWMS001) also demonstrated benefit on sleep disturbance ( $p = 0.047$ ) (Fig. 2). A cohort of those patients continued into a prolonged SAFEX study with continued improvement in various other MS-associated symptoms with stable or even decreasing Sativex dosages (12)(Fig. 3)

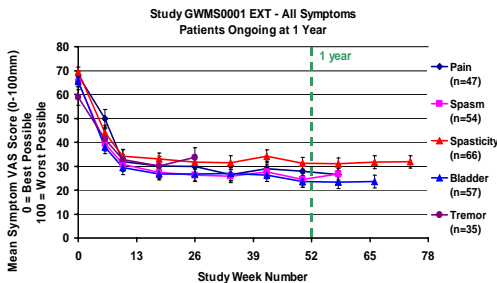


Figure 3: MS symptoms in a SAFEX Study (GWMS0001 EXT).

A available data from long-term safety extension (SAFEX) studies in 154 subjects with central and peripheral neuropathic pain confirm continued efficacy of Sativex in maintaining improvements in subjective sleep parameters (Fig. 4).

Study GW EXT0102 Sleep Quality

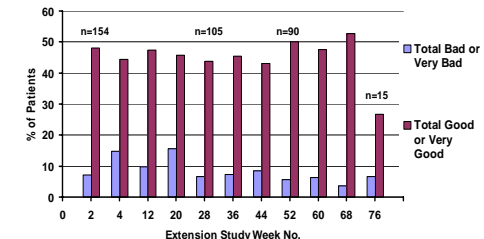


Figure 4: Cumulative Phase II-III data on sleep disturbances in a long term SAFEX study of neuropathic pain patients treated with Sativex.

No dose escalation over time was manifest, supporting a total lack of tolerance to clinical benefit of Sativex sleep or other symptoms (13). Some 40-50% of subjects attained good to very good sleep quality with maintenance for up to two years.

## Discussion

Cannabis extracts, particularly with the inclusion of cannabidiol, seem to have a unique ability to improve subjective sleep in patients with MS and NP, with symptomatic relief of pain, spasms, nocturia and related complaints. Many CBM patients remarked how the medicine had transformed their lives through its ability to allow them more restful sleep, increase their daytime level of function, and markedly improve their quality of life. In the context of clinical usage of Sativex, evidence to date would consistently support the observation that standardized oromucosal cannabis based medicines produce effective improvement in sleep parameters and satisfaction without major changes in EEG sleep architecture, do so consistently over time without evidence of tolerance, and without unusual sequelae. Their addition to the pharmacopoeia should be welcomed by patients, families and physicians.

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