**Objective**

This presentation reports results of Phase I-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).

**Design/Methods**

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 dose 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 less cannabis like 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 neuropathic symptoms (p<0.05)(Study GWNP0101)(Fig. 2). Patients demonstrated a surprising conversion of subjective sleep from poor or fair to good quality (p<0.001), and sleep duration (p<0.001)(Study GWNP0102A)(Fig. 2). Patients with intractable lower urinary tract symptoms (LUTS) due to MS also showed significant improvement in self-assessment (p<0.05)(7).

In a Phase III randomized placebo controlled trial in central neuropathic pain due to MS in 5 weeks 68 patients, significant benefit of Sativex over placebo was observed in sleep disturbance (p<0.003)(Study GWMS0001)(Fig. 2). A Phase III trial in intractable pain in 79 subjects (Study GWBP0101)(8) also showed a strong trend toward benefit on sleep (p=0.045)(Fig. 2). In a Phase III randomized placebo controlled study of 65 Sativex subjects with peripheral neuropathic pain characterized by akathisia produced more marked reductions in sleep disturbance (p<0.001)(Study GWNP0107)(Fig. 2). In the largest clinical study of brachial plexus avulsion and central neuropathic pain to date (10)(Study GWPB0101), in 46 subjects in a double-blind crossover design of placebo vs. oralomucol THC CBM (Tetranabinex®) vs. Sativex, sleep parameters diverged from a baseline of 4.8 to 5.2 with placebo (NS), to 6.9 with Tetrabamex (p<0.001) and 5.9 with Sativex (p=0.017)(Fig. 2).

**Results**

Patients were studied employing CBM in self-identified 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 doses and symptoms. After initial Phase I studies, improvements in sleep quality in clinical trials were based on subjective self-assessments, such as number of waking episodes.

**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, ∆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 (Tetrahydrocannabinol®). 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 5% (w/w) of the total BDS (1). Minor cannabinoids are present (5 – 6%). The remainder of the BDS consists of terpenes (8 – 7%, most GRAS (Generally Recognized as Safe), α-terpinene, β-pinene, α-selinene, α-selinene, α-pinene, β-caryophyllene, limonene, β-myrcene, β-sabinene, sabinene, linalool, camphene, β-caryophyllene, and other minor components (also GRAS) derived from the plant material (2). The most significant cannabidiol and non-cannabinoid components are controlled within the BDS specification. BDS is formulated into a spray for sublingual and oro-pharyngeal administration. Each 100 µL pump-action spray contains 2.7mg of THC and 2.5mg of CBD, the minor components, plus ethanol: 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 200 subjects with neuropathic pain were examined for the purposes of this study.

**Discussion**

Cannabis extracts, particularly with the inclusion of cannabinoid, seem to have a unique ability to improve subjective sleep in patients with MS and NP, with symptomatic relief of pain, spasm, nocturnal and residual complaints. Many CBM patients remarked on 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 cannabis based medicines produce effective improvement in sleep parameters and satisfaction without major changes in EEG sleep architecture, do so consistently over time with evidence of tolerance, and without unusual sequelae. Their addition to the pharmacopoeia should be welcomed by patients, families and physicians.

**References**