Double-blind, Randomised, Placebo Controlled, Parallel Group Study of Sativex® in the Treatment of Patients With Peripheral Neuropathic Pain, Associated With Allodynia

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» INTRODUCTION

Peripheral Neuropathic Pain (PNP):

- Management of PNP is a significant challenge;
- Currently the most difficult pain to treat;
- Current therapies have a limited effect on PNP and can cause side effects;
- Recent research indicates that cannabinoids have therapeutic potential[1,2];
- This study aimed to evaluate the long term efficacy of Sativex in relieving chronic PNP and to assess the safety of Sativex in study patients with PNP associated with allodynia.

Study drug: Sativex® (THC:CBD) endocannabinoid system modulator

- Derived from highly standardised botanical extract;
- Formulated into a spray for sublingual/oromucosal administration;
- Highly standardised formulation, each 100µl spray of Sativex® contains 2.7 mg Δ^9-tetrahydrocannabinol (THC), 2.5mg cannabidiol (CBD), and small amounts of other cannabinoids;
- Approved in Canada for relief of central neuropathic pain in MS and cancer pain.

» METHODS

- A 15-week (one-week baseline and 14-week treatment period), multicentre, double blind, randomised, placebo controlled parallel group study;
- Patients randomised to either Sativex or placebo and self-titrated study medication based on efficacy and tolerability, up to a maximum of 24 sprays/day;
- Patients had chronic (≥six months) PNP associated with allodynia, and secondary to post-herpetic neuralgia, peripheral neuropathy or focal nerve lesion or Complex Regional Pain Syndrome type 2.

Primary Endpoints:

- Change from baseline in 0-10 numerical rating scale (0-10 NRS) pain severity scores
- Responder analysis (≥30% decrease in 0-10 NRS pain severity score from baseline)

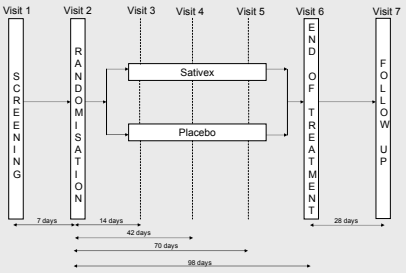
Secondary Endpoints:

- Neuropathic pain scale (NPS)
- Brief pain inventory (BPI)
- Sleep quality 0-10 NRS
- Rescue analgesic use
- Subject global impression of change (SGIC)
- Quality of life questionnaire (EQ-5D)

Safety Endpoints:

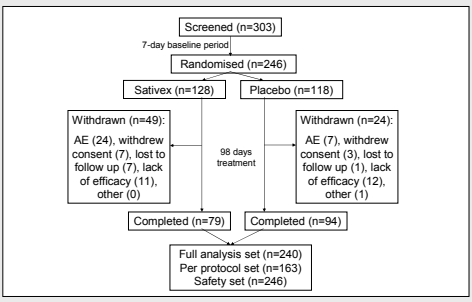
- Adverse Event (AE) monitoring

Study Schema



» RESULTS

PATIENT DISPOSITION

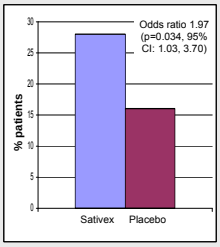


The two treatment groups were closely matched for all demographic and baseline characteristics.

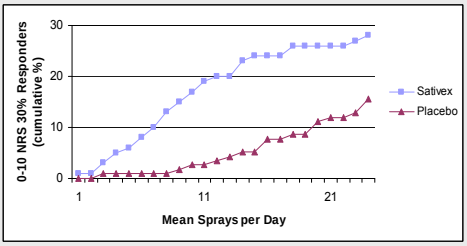
PRIMARY ENDPOINTS

- The pain responder analysis was statistically significant in favour of Sativex with an odds ratio of 1.97.
- The change in pain 0-10 NRS from baseline was -1.05 for Sativex and -0.71 for placebo (-0.34 treatment difference in favour of Sativex), but this was not statistically significant.
- For 30% responders, the proportion of responders was observed to increase much more quickly in relation to the dose of Sativex compared with placebo (illustrated below). Explain better??
- At around 14-15 sprays per day, the response rate in patients receiving Sativex began to slow down whilst for those taking placebo, the proportion of responders was still increasing maximally.

0-10 NRS Pain Scores: Responder Analysis – Proportion of patients with at least a 30% improvement from baseline in the primary evaluable period



Cumulative Percent at the 30% Response by Mean Sprays



SECONDARY ENDPOINTS

Sleep Quality Assessment

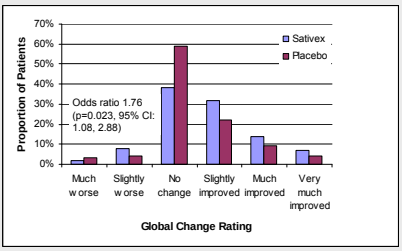
- The adjusted mean sleep quality rating score for the Sativex group showed an improvement of 1.57 points from a mean baseline score off 5.4 points, compared with an adjusted decrease of 0.74 points from a baseline of 5.8 points for placebo.
- The estimated treatment difference of -0.83 points in favour of Sativex was highly statistically significant (p=0.01).

Rescue Analgesic Use

- On average, the Sativex group used fewer doses of rescue analgesic than the placebo group.
  - •X (SD) vs. Y (SD)
- On average , the Sativex group used fewer spray of study medication than the placebo group.
  - •X (SD) vs. Y (SD)

SGIC

- There was a statistically significant treatment difference for a positive response in favour of Sativex.



SAFETY ENDPOINTS

Adverse Events

- Study medication was well tolerated
- Most AEs were mild or moderate in severity and resolved
- The most commonly reported treatment related AEs were dizziness, nausea and fatigue
- AEs were the commonest reason for study withdrawal (24 [33%] Sativex patients vs 7 [10%] placebo patients)
- There were no treatment-related serious AEs

» DISCUSSION

- Patients taking Sativex obtained clinically important improvements in their pain and quality of sleep over and above currently available treatments
- This was achieved in a meaningful proportion of otherwise treatment-resistant patients
- The difference in analgesic effect between Sativex and placebo was smaller than previously observed, possibly due to
  1. A higher use of rescue analgesic use in the placebo group compared with the Sativex group;
  2. The very high placebo response seen, which increased maximally as the number of sprays increased

» CONCLUSION

- **These data support the efficacy of Sativex in relieving PNP and substantiate its safety profile in patients**
- **Sativex improved both the pain and sleep parameters measured**
- **There were no signs of tolerance; pain relief was maintained without an increase in dose**

REFERENCES: [1]Rog D, Nurmikko T, Friede T, Young C. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology 2005;65:812-819; [2]Nurmikko ", Serpell M, Hoggart B et al. Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. Pain 2007;133(1-3):210-220.

CONFLICT OF INTEREST: This trial was sponsored and fully funded by GW Pharma Ltd. Investigators received research grants to cover the costs of the study.