Stable dose cannabinoid medicine (Sativex®, THC+CBD) can provide sustained efficacy in the treatment of refractory painful diabetic neuropathy or other peripheral neuropathic pain associated with allodynia.

Ratcliffe S[1], Serpell MG[2], Hoggart B[3], Simpson K[4]

[1]MAC UK Neuroscience Ltd., Blackpool, UK; [2]Gartnavel General Hospital, Glasgow, UK; [3]Solihull Hospital, Solihull, UK; [4]Seacroft Hospital, Leeds, UK.

» BACKGROUND

Neuropathic Pain (NP) poses a major challenge:

- Most common long-term complication of diabetes mellitus
- Leads to great morbidity and mortality
- Results in a huge economic burden for diabetes care
- Can be a disabling and painful symptom
- Existing treatments afford only partial relief and have unpleasant side-effects

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

- Approved in Canada for relief of central neuropathic pain in Multiple Sclerosis and cancer pain
- Produced from selected strains of cloned Cannabis sativa plants formulated into a spray for oromucosal administration
- Highly standardised formulation: each 100µl spray of Sativex® contains 2.7 mg delta-9-tetrahydrocannabinol (THC), 2.5 mg cannabidiol (CBD), minor cannabinoids (5-6%) and small amounts of other plant extracts such as terpenes
- Subjects self-titrated to their optimal dose on the basis of their individual efficacy and tolerability response, up to a maximum of 24 sprays/day

Rationale for Treatment:

- Previous clinical trials have shown that Sativex has analgesic properties that are effective in relieving neuropathic pain
- These studies also suggested that Sativex is well tolerated and may also improve sleep and quality of life
- Pain resulting from diabetic neuropathy is often not satisfactorily alleviated by existing therapies

» METHODS

Study Design:

- 38-week open label, follow-on study

Study Objectives:

- To evaluate maintenance of effect and development of tolerance through exposure to, and safety of open label Sativex therapy in subjects with peripheral neuropathic pain (PNP)

Study Population:

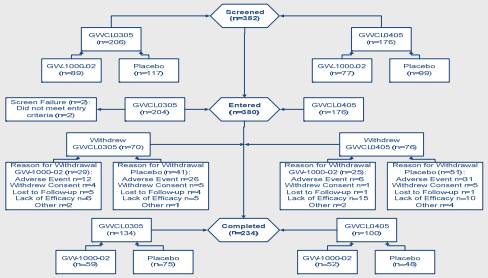
- 380 subjects who had participated in one of two 3-month (GWCL0305 and GWCL0405), double blind, randomised controlled clinical trials (parent RCT) designed to investigate the role of Sativex in the treatment of PNP secondary to diabetes or associated with allodynia

Assessments:

- Primary endpoint was pain severity scores recorded using a 0-10 Numerical Rating Scale (NRS-11)
- Secondary endpoints included theNeuropathic Pain Scale (NPS), sleep disturbance NRS-11, Subject Global Impression of Change (SGIC), intoxication NRS-11 and a quality of life EQ-5D health questionnaire
- Safety was assessed by monitoring adverse events (AEs) and serial clinical chemistry and vital signs

» RESULTS

1. Disposition of Subjects

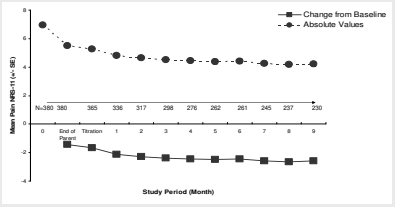


2. Baseline Subject Characteristics

		No. of Subjects (%) (n=380)
Gender	Male	200 (53%)
	Female	180 (47%)
Ethnic Origin	White/Caucasian	374 (98%)
	Other	6 (2%)
Previous Cannabis Use (at any time, prior to parent RCTs)		38 (10%)
		Mean (SD)
Age (years)		57.8 (12.03)
BMI (kg/m^2)		29.9 (6.76)
Duration of Any Underlying Condition Causing PNP (years)		9.63 (8.45)
Duration of PNP (years)		5.35 (5.30)

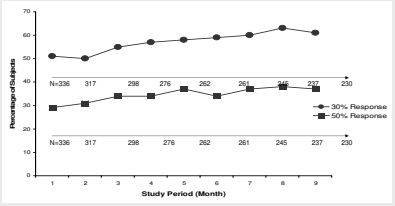
3. Mean NRS Pain Scores

There was an improvement over the initial weeks of treatment and subsequent maintenance of benefit.

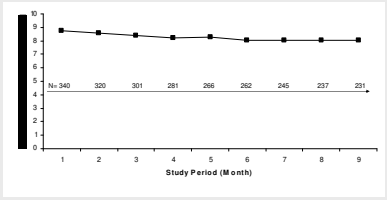


4. Responders at the 30% and 50% Level of Improvement

After 9 months of open label Sativex treatment, 141 (61%) completing subjects reported pain scores that were improved by ≥30% from the parent RCT baseline 12 months earlier



5. Dosing Data



6. Secondary Endpoints

NPS and Sleep Quality NRS-11

- Improvement maintained with time and continued to improve up to week 26 (change from parent RCT baseline was -21.51 for the NPS and -2.39 for the sleep NRS-11)

SGIC

- 70% of subjects had an improvement in nerve pain
- 8% of subjects had a worsening in nerve pain

Health Outcomes – EQ-5D Questionnaire Score

- Descriptive System Questionnaires (Mobility, Activity, Self care, Pain and Anxiety):
  - -More subjects improved than worsened in their classification form parent RCT baseline
- Weighted Health State Index and Health Status VAS:
  - Small improvement in both index and VAS scores, maintained at final visit

Intoxication Scores

- Mean intoxication scores throughout course of study were less than 2 points out of 10

7. Safety

Common adverse events (occurring in 5% or more subjects)

System Organ Class / Preferred Term	All-Causality Number (Percentage) of Subjects	Treatment-Related Number (Percentage) of Subjects
Total subjects with at least one AE	**295 (78%)**	**224 (59%)**
Nervous System Disorders	**168 (44%)**	**140 (37%)**
Dizziness	79 (21%)	74 (19%)
Dysgeusia	29 (8%)	28 (&%)
Somnolence	28 (7%)	27 (7%)
Headache	23 (6%)	11 (3%)
Gastrointestinal Disorders	**135 (36%)**	**97 (26%)**
Nausea	42 (11%)	35 (9%)
Dry Mouth	30 (8%)	29 (8%)
Vomiting	25 (7%)	11 (3%)
General Disorders and Administration Site Conditions	**92 (24%)**	**69 (18%)**
Fatigue	31 (8%)	27 (7%)
Feeling Drunk	21 (6%)	21 (6%)
Psychiatric Disorders	**79 (21%)**	**55 (14%)**
Disorientation	19 (5%)	18 (5%)

- 295 subjects reported at least 1 treatment-emergent AE; 224 subjects (59%) were related
- 88 subjects (23%) reported at least 1 AE leading to permanent cessation of study medication.
- Severe AEs affected 87 subjects (23%).
- 40 subjects (11%) reported at least one SAE; 4 subjects (1%) were related:
  - 2 subjects experienced amnesia, 1 resolved following discontinuation of Sativex and 1 was still ongoing at last visit; 1 subject experienced paranoia which resolved following discontinuation of Sativex; 1 suicide attempt occurred 26 days after last dose.
- 2 fatal non-related AEs occurred.

» CONCLUSION

- Sativex remained well tolerated and beneficial for the majority of subjects with peripheral neuropathic pain secondary to diabetes or associated with allodynia over nine months.
- Maintenance in pain relief was achieved without an increase in dose of Sativex.
- The study raised no new safety concerns for Sativex.