

Sativex[®] MS Neuropathic Pain Trial



Study GWMS0501

8 April, 2008



Study GWMS0501

- Study title:
 - Sativex in the treatment of neuropathic pain in people with MS
- Background to the study
 - Strong pharmacological basis for effect of THC and CBD
 - Previous study shows highly significant efficacy for Sativex in MS neuropathic pain*
 - Health Canada has granted approval in this indication
 - Efficacy of Sativex also shown in other models of neuropathic pain
 - Allodynia (GWNP0101⁺ and GWCL0405)
 - Brachial plexus avulsion (GWBP0101[#])
- Role of study in Sativex strategy
 - Expand target EU indications for Sativex to include MS pain
 - Provide additional evidence of efficacy in MS pain to Health Canada

*Rog D et al, *Neurology* 2005: #Berman J et al, *Pain* 2004: + Nurmikko T et al *Pain* 2007

Study Design

General:	Placebo-controlled, randomised, parallel group study
Patients:	People with Multiple Sclerosis and neuropathic pain who have failed to gain adequate relief from existing analgesia
Duration:	14 weeks post-randomisation
Endpoint:	Responder analysis ($\geq 30\%$) based on the 0-10 Numeric Rating Scale
Data collection:	IVRS

Note: Following a detailed analysis of 2 other reported studies in Jan 07, GW introduced a protocol amendment to limit the maximum permitted dose of study medication to 12 sprays per day and slowing rate of dose titration

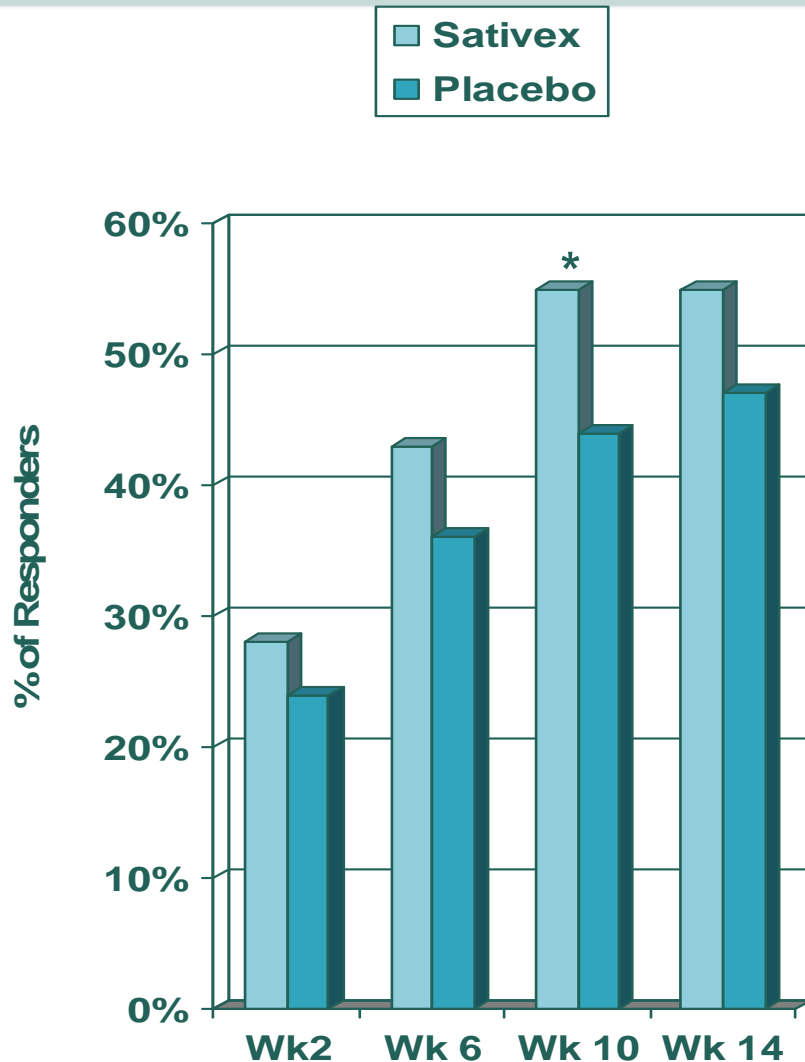
Results: Demographics

	Sativex (n=167)	Placebo (n=172)
Age	48.4 years	49.5 years
Gender - Male	32%	32%
- Female	68%	68%
Type of MS		
Relapsing-Remitting	48%	45%
Primary Progressive	11%	13%
Secondary Progressive	39%	41%
Progressive-Relapsing	2%	1%
Duration of MS	11 years	13 years
Duration of Neuropathic Pain	5.6 years	5.3 years
Baseline EDSS	5	4.9
Mean Baseline Pain (0-10 NRS)	6.55	6.61

Groups well-matched at baseline

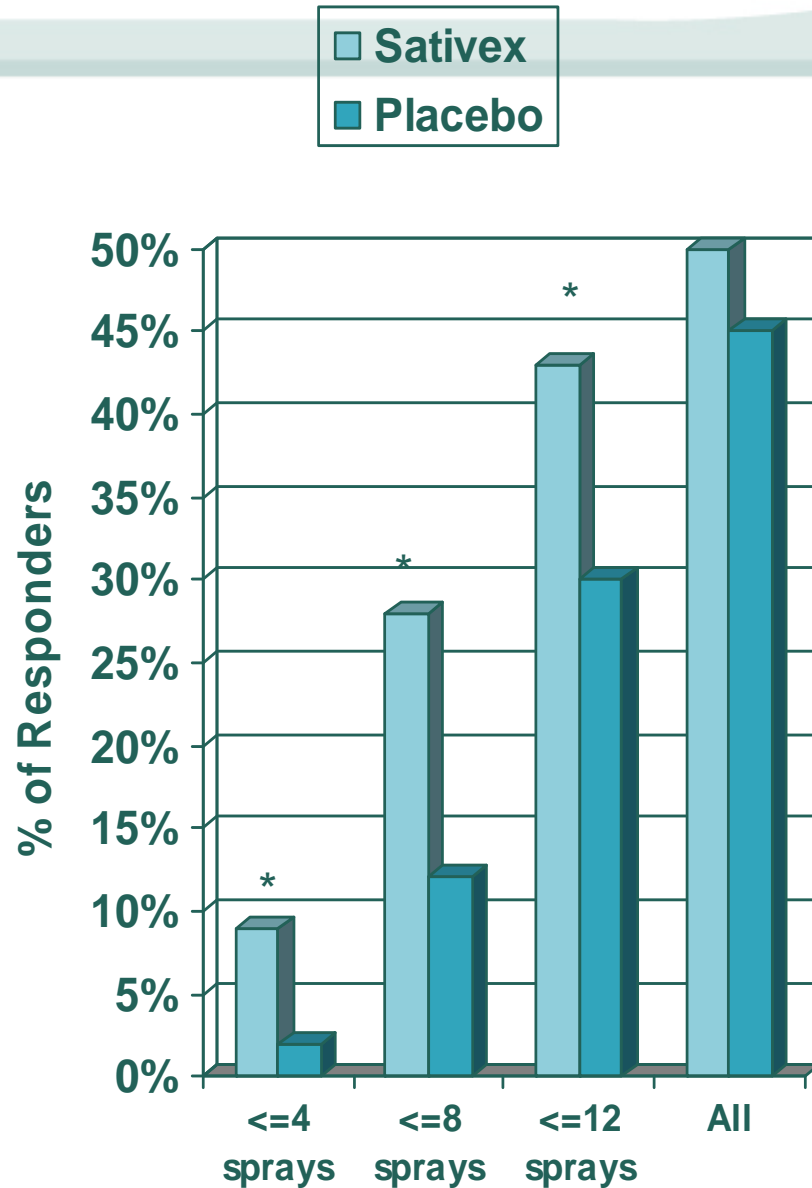
Study GWMS0501: Primary Analysis

30% Responders by time (observed cases)



- Gradual improvement with time on Sativex
- Sativex consistently numerically superior to placebo throughout study
- Primary endpoint is statistically significant at Week 10
- Marginal change in placebo arm between Weeks 10 & 14 leads to loss of statistical significance

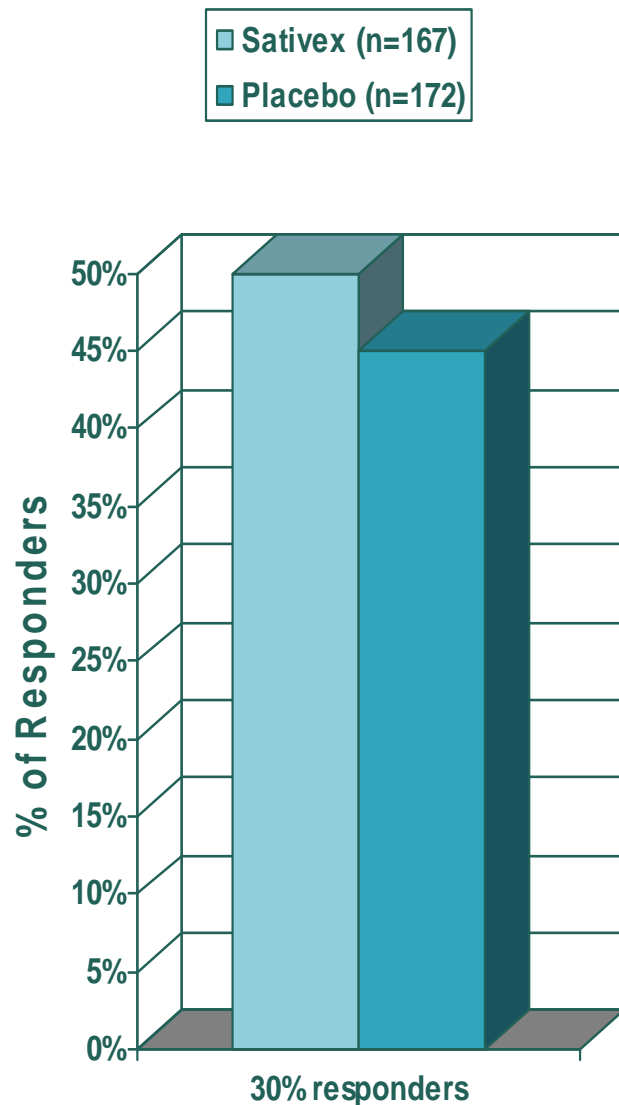
Study GWMS0501: Primary Analysis Highly Significant Result at Equal Doses



- At doses of 4, 8 and 12 sprays, Sativex is highly significantly superior to placebo
- A disproportionate number of placebo responders occur at high doses
- A disproportionate number of placebo patients take high doses
- Mean daily dose at study end was less than 9 sprays on Sativex and 12 sprays on placebo

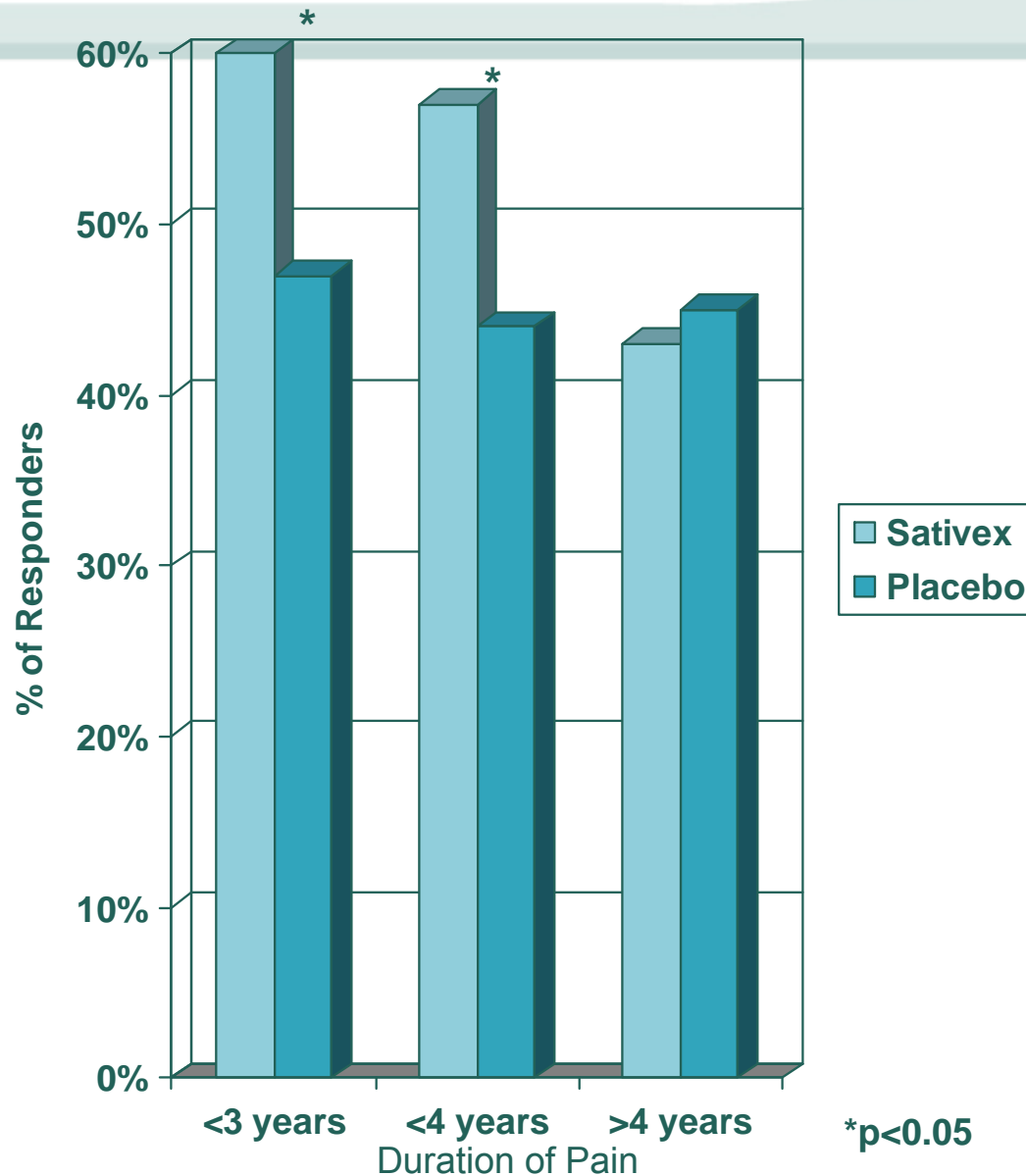
*p<0.01

Study GWMS0501: Primary Endpoint



- 30% improvement is recognised as clinically relevant
- Very high response to Sativex
 - Similar to previous MS pain study
 - Second largest seen with Sativex
 - Superior to published studies of other agents
- Unexpectedly high placebo response
 - Largest seen
- Responder analysis at 30% and at 50% is in favour of Sativex but did not reach statistical significance
- Secondary efficacy is consistent with primary efficacy

Study GWMS0501: Responders by Duration of Pain



- 50% of patients in the study had more than 4 years duration of pain
- Patients with shorter pain duration respond significantly better than placebo

Study GWMS0501: Protocol Amendment - Rationale

- Jan 2007: Sativex neuropathic pain studies reported which show that, when given freedom to self-titrate, placebo patients use almost twice as many sprays per day than Sativex
 - At higher numbers of sprays, placebo patients continue to respond
 - This dilutes the difference seen between Sativex and placebo overall
- Early withdrawals due to adverse events occurred in prior studies
 - This harms the Last Observation Carried Forward (LOCF) analysis

This amendment:

1. Introduced a slower titration rate with the aim of reducing early withdrawals
2. Reduced maximum daily dose from 24 sprays to 12, with the aim of reducing the difference in number of sprays between Sativex and placebo
 - amendment submitted in Jan 07 – implemented March 07

Lowest Withdrawal Rates

Withdrawals on Sativex = 16% (9% due to AEs)

Withdrawals on placebo = 9% (6% due to AEs)

Previous studies of similar duration showed higher withdrawal rates

Study	Sativex	Placebo
Allodynia	39%	20%
Diabetic Neuropathy	29%	16%

Favourable Adverse Event Profile

	Sativex	Placebo
Any Adverse Event	72%	62%
Serious Adverse Events	8	8
Deaths	0	1

Adverse events occurring in 10% or more of patients		
Dizziness	20%	8%
Fatigue	11%	8%
Nausea	11%	6%
Somnolence	10%	2%

Superior safety profile to that seen in earlier studies

Significant improvement in “risk-benefit” equation

Conclusions from GWMS0501

- Sativex has provided highly meaningful improvements in otherwise treatment-resistant patients
 - One of the largest seen for any pain study
 - Consistently superior to placebo
- Unexpectedly large placebo effect
- Large placebo effect leads to loss of statistical significance
 - Related to substantial differences in daily dose
- The protocol amendment was aimed at reducing the difference in Sativex and placebo dosing
 - It achieved its objectives to an extent – but failed to reduce sufficiently the dosing difference
- Allowing patients to determine their own dose with a subjective end-point confounds the results
- Patients with shorter pain duration do better
 - Long pain duration may lead to irreversible nerve damage
- Slower dose titration enhances safety profile and reduces withdrawal rate

What does this mean for ongoing and future studies?

1. MS Spasticity

- No within-patient dose titration permitted
- Patients with shorter duration of disease are recruited
- Non-responders to Sativex are excluded

2. Cancer Pain

- No within-patient dose titration
- Three distinct fixed target dose groups
 - Each with their own placebo

Conclusions

These studies are not subject to the confounding influence of allowing patients to ‘control’ their own dose.

The study design of these ongoing studies is further validated by today’s results.

The comparison between Sativex and placebo at equivalent doses shows positive results in all Sativex studies to date.

Our confidence in their outcome is not affected by these results

Sativex Regulatory Strategy

- Recent EU regulatory submission related to MS spasticity and the route to approval in this indication is established
 - Phase III MS spasticity study ongoing and due to report later in 2008
- Lead US indication is cancer pain
 - Phase IIb/III study underway
- Further studies planned in MS neuropathic pain and peripheral neuropathic pain