CENTRE HOSPITALIER REGIONAL
UNIVERSITAIRE DE LILLE

Université Lille Nord de France
Pôle de Recherche
et d'Enseignement Supérieur

GSEP
Groupe Septentrional d'Etudes
et de recherche
sur la sclérose en Plaques

# Cannabis in the management of MS symptoms

Patrick Vermersch
University of Lille Nord de France
19 May 2012
EMSP Annual Congress

# 10 most common MS-related symptoms (from a survey of 2265 patients)

| Symptom | Patients experiencing the symptom (%) | Patients rating symptom as moderate to severe (%) |
|---|---|---|
| Fatigue | 96 | 88 |
| Balance/dizziness | 92 | 74 |
| Loss of mobility | 91 | 79 |
| Sensory | 88 | 54 |
| Bladder problems | 87 | 70 |
| Loss of memory/concentration | 87 | 52 |
| Spasticity | 82 | 54 |
| Visual disturbances | 82 | 41 |
| Pain | 81 | 50 |
| Bowel problems | 74 | 45 |

Hemmett et al. *Q J Med* 2004; 97: 671-76.

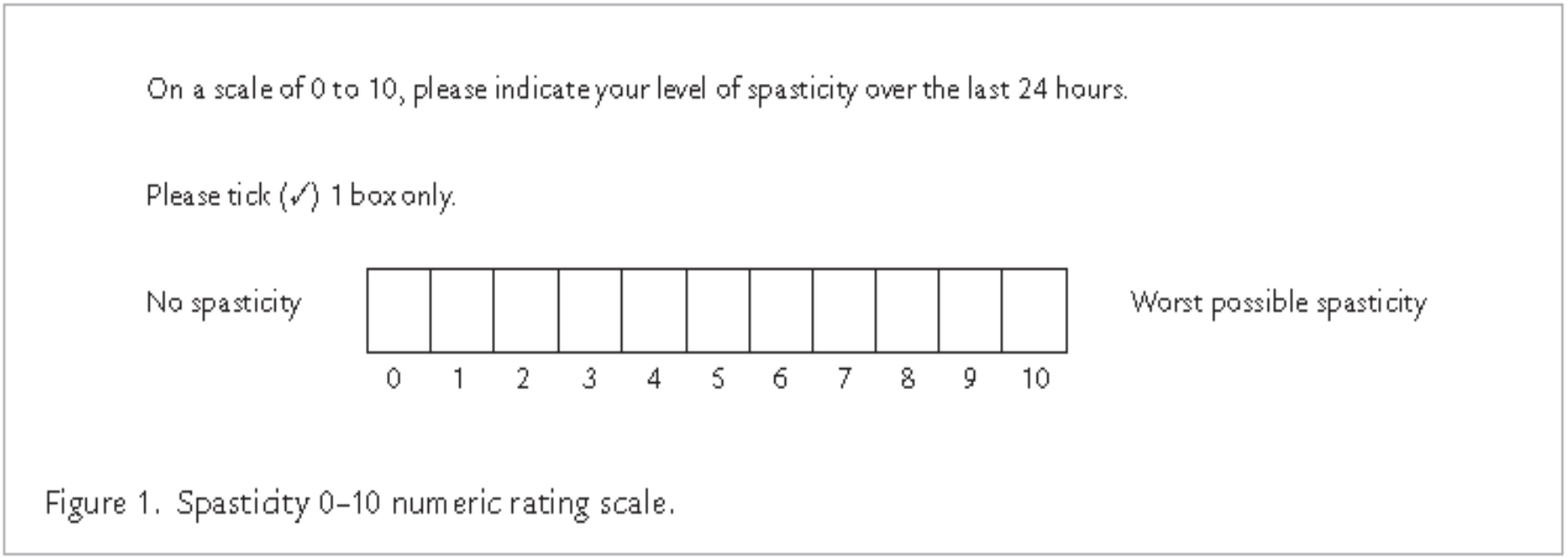
# Ashworth scale is the most commonly used scale to measure spasticity

| Score | Modified Ashworth Scale |
|---|---|
| 0 | No increase in muscle tone |
| 1 | Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part(s) is moved in flexion or extension |
| 1+ | Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the range of movement (ROM) |
| 2 | More marked increase in muscle tone through most of the ROM, but affected part(s) easily moved |
| 3 | Considerable increase in muscle tone, passive movement difficult |
| 4 | Affected part(s) rigid in flexion or extension |

- Limitations: lack of sensitivity, reliability and validity

Farrar et al. *J Neurology* 2007; Anwar & Barnes *NeuroRehab* 2009.

# Numerical Rating Scale (NRS) is a valid alternative for measuring spasticity


On a scale of 0 to 10, please indicate your level of spasticity over the last 24 hours.

Please tick (✓) 1 box only.

No spasticity

0 1 2 3 4 5 6 7 8 9 10

Worst possible spasticity

Figure 1. Spasticity 0–10 numeric rating scale.

- Symptom severity is estimated by the patient, over the preceding 24 hours, and recorded daily
- It is more reliable and sensitive than the Ashworth scale for reporting spasticity symptoms

Farrar et al. *J Neurology* 2007; Anwar & Barnes *NeuroRehab*.

# MS spasticity: conclusions

- Spasticity is one of the most disabling symptoms associated with MS.
- Like all MS symptoms, spasticity occurs as a result of myelin and nerve fibre degradation.
- **Unmet need**: spasticity in MS progresses despite available treatments, many patients (and physicians) judge the treatment for spasticity as unsatisfactory
- The Ashworth scale is the most widely used rating scale for assessing the degree of spasticity.
- The NRS is a valid and sensitive diagnostic tool for determining the severity of spasticity.

# Cannabinoids in the treatment of MS Spasticity

# Medicinal use of cannabis

- Cannabis has a long-history of use as both a medicine and as a recreational drug.
- Medicinally, street cannabis has been used to utilise it's antispastic, muscle relaxant and pain relief effects.
- In a UK survey of persons using cannabis medicinally (mostly smokers) between 1998 and 2002, almost 75% indicated that it was better or somewhat better than their previous treatment for MS or various pain states.

**Ware et al. *Int J Clin Pract* 2005;59: 291-95.**

# Street cannabis: concerns/limitations

- Legal issues.
- Street cannabis lacks standardization and purity.
- In recent herbal samples high levels of THC (psychoactive cannabinoid) and low levels of CBD (antipsychotic cannabinoid) were reported .
- Largely smoked and this increases the risk of lung cancer, heart disease, etc.
- Smoked cannabis has variable pharmacokinetics, causing very high THC peaks, which lead to psychoactivity and other adverse events.

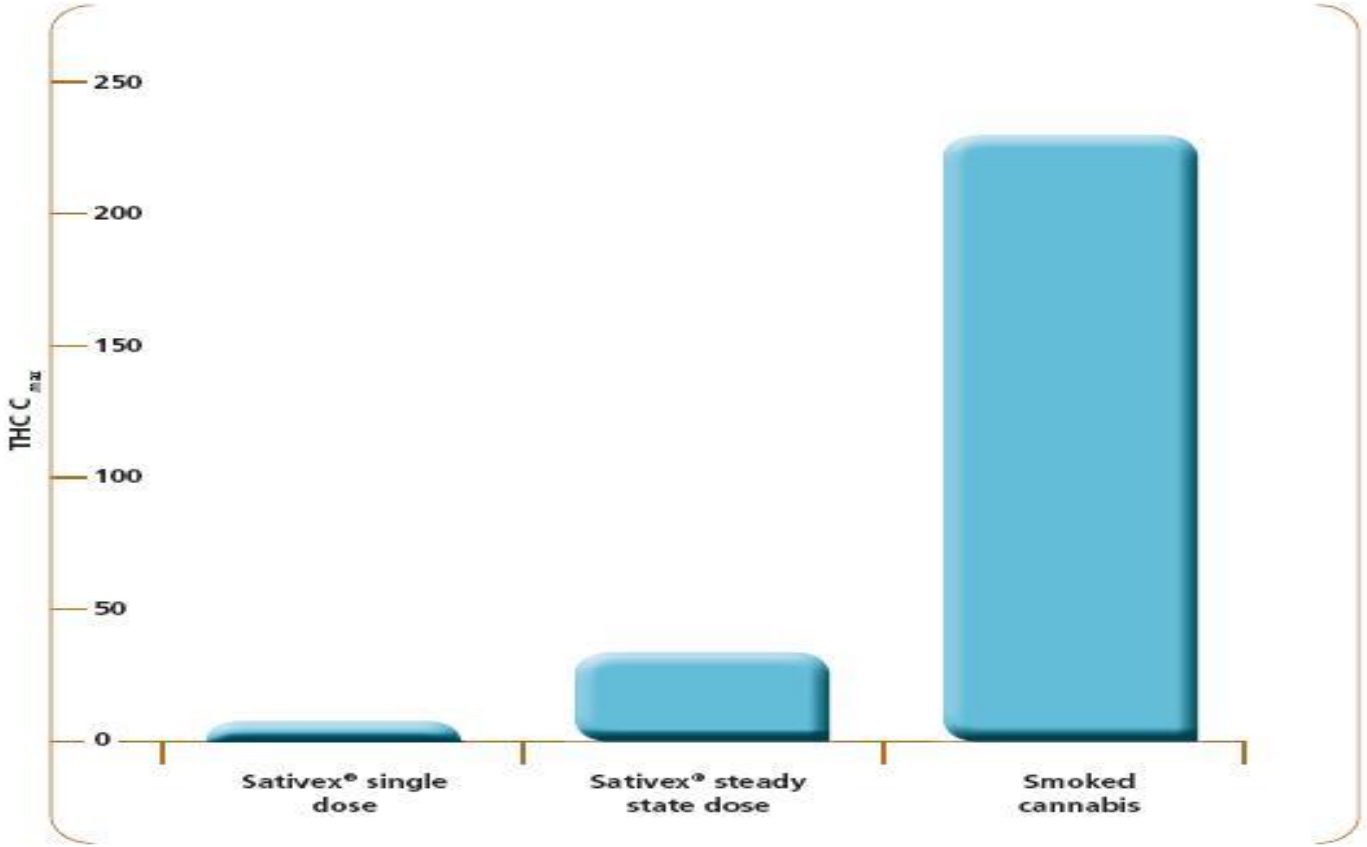
**Chong et al. *Mult Scler* 2006; 12: 646-51.; Wade et al. *Mult Scler* 2006; q12: 639-45.; Aldington et al. *Eur Resp J* 2008; 31: 280-86.; Potter et al. *J Forensic Sci* 2008; 53: 90-4.**

# Rationale for the development of Sativex

- To produce a standardised medicinal product based upon the main active constituents of *Cannabis sativa,* tetrahydrocannabinol (THC) and cannabidiol (CBD).
- Formulated to ensure purity and stability.
- To administer in a way (oromucosal) which provides a satisfactory pharmacokinetic profile avoiding the high plasma levels and risks associated with smoking.
- To benefit from the synergistic interaction between CBD and THC, with a reduction in psychoactivity and enhanced cannabinoid-mediated clinical effects.

**Perez *Drugs of Today* 2006; 42: 495-501; Potter et al. *J Forensic Sci* 2008; 53: 90-4.**

# Maximum plasma THC levels with Sativex and Street Cannabis (smoked)




**Guy & Stott In Parnham et al. (eds) Milestones in drug therapy: cannabinoids as therapeutics, 2005.**

# Cannabinoids: conclusions

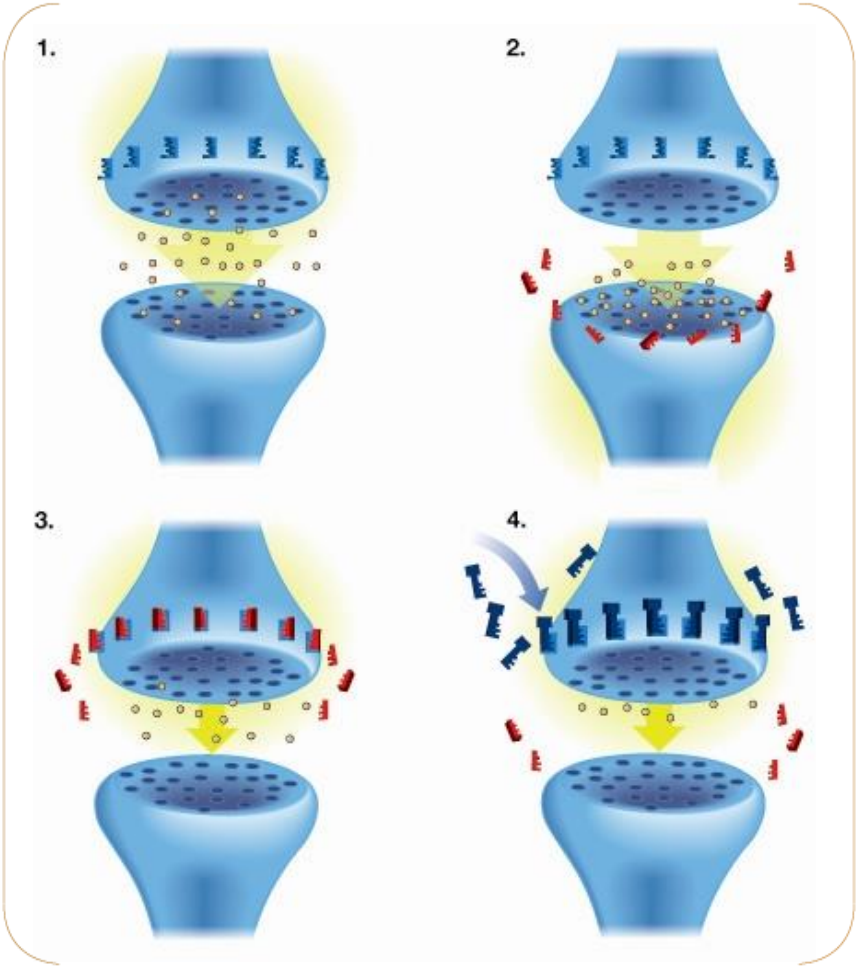
- Street cannabis lacks standardization and purity.
- Smoking cannabis results in very high THC peaks, which lead to psychoactivity and other adverse events, and also increases the risk of abuse.
- Sativex was developed to produce a standardised medicine based upon the active constituents of *Cannabis sativa,* THC and CBD. The formulation and oromucosal route of delivery ensure a pharmacokinetic profile which avoids the problems associated with high peaks of THC.

# Sativex: the product

- Sativex is an endocannabinoid system modulator.
- It is a unique cannabinoid-based medicine derived from the active principles of *Cannabis sativa.*
- The pharmaceutical form is prepared from 2 cloned chemovars of *C. sativa* to ensure standardisation and quality.
- One clone produces high levels of 9-delta-tetrahydrocannabinol (THC) and the other high levels of cannabidiol (CBD).
- These 2 cannabinoids account for about 70% of the composition of Sativex; the remaining 30% comprises minor cannabinoids, terpenoids, sterols and triglycerides

**Perez *Drugs of Today* 2006; 42: 495-501; SmPC Sativex Oromucosal Spray 2010.**

# Cannabinoids: mechanism of action




CNS forum. Cannabinoid receptors 2009.

1.A nerve impulse reaching the synapse stimulates the release of neurotransmitters (the yellow molecules). These cross the synapse and bind to receptors on the post-synaptic cell, initiating a series of events.

2.One of these events is the release of endocannabinoids (the red molecules) which are released locally, crossing the synapse in the opposite direction of the nerve impulse.

3.The endocannabinoids bind to pre-synaptic $CB_1$ receptors (the light blue receptors) inhibiting the release of further neurotransmitters, whether the neurotransmitters are inhibitory (e.g., GABA) or excitatory (e.g., glutamate). This is an example of negative feedback system.

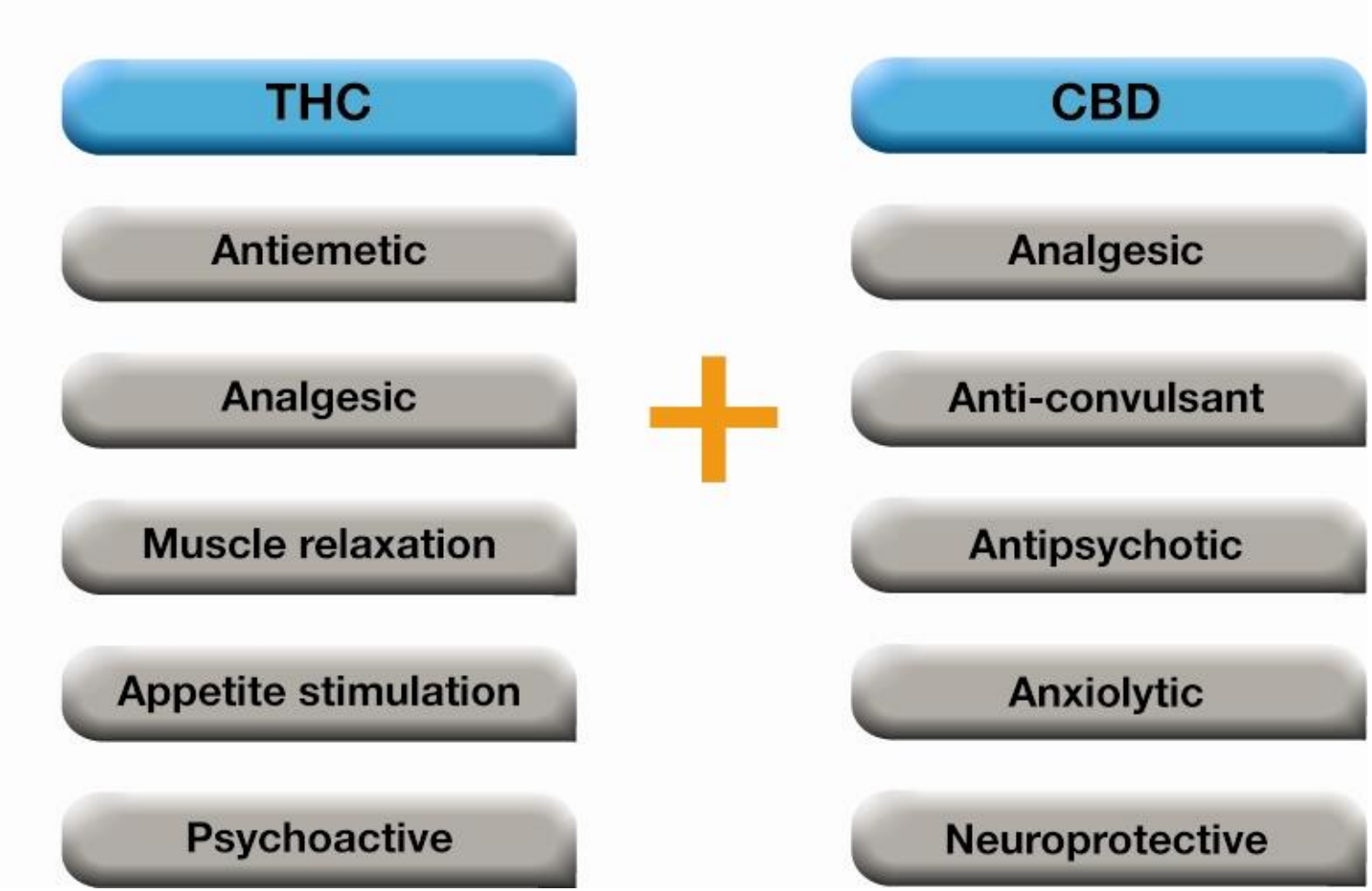
4. Phytocannabinoids mimic the action of these endocannabinoids. In this way, they are able to augment the effect that endocannabinoids have in regulating the transmission of impulses from one nerve to another.

# THC and CBD: mechanism of action

- THC is a partial agonist of both $CB_1$ and $CB_2$ receptors.
- It has greater activity at $CB_1$ subtypes which is thought to account for its psychoactivity.
- CBD has lower affinity for both receptors and is an antagonist at the $CB_1$ receptor.
- CBD may act synergistically with THC, antagonizing psychoactive and sedative effects, but enhancing cannabinoid-mediated clinical effects.

**Potter et al. *J Forensic Sci* 2008; 53: 90-4.**

# THC and CBD: synergy (complementary effects)




Russo & Guy *Med Hypotheses* 2006; 66: 234-46.

# Mechanism of action: conclusions

- THC is a partial agonist of $CB_1$ and $CB_2$ receptors while CBD is a $CB_1$ antagonist.
- THC has greater activity at $CB_1$ subtypes which accounts for its psychoactivity.
- CBD antagonizes the effects of THC at $CB_1$ receptors.
- Thus, the combination of THC + CBD may interact synergistically: reducing psychoactivity and increasing clinical effects.

# Sativex: pharmacokinetics

- Following administration THC and CBD are rapidly absorbed and appear in the plasma within 15 mins.
- Pharmacokinetic parameters vary between patients, highlighting the importance of individual dosage titration.
- Cannabinoids are highly lipophilic, quickly absorbed into body fat.
- Plasma concentrations following oromucosal administration are lower than those after inhalation because absorption is slower and redistribution into fat is rapid.
- THC and CBD are metabolised in the liver.
- Cannabinoid elimination is biphasic with an initial half-life of about 4 hours and a terminal half-life of 24-36 hours.

**SmPC Sativex Oromucosal Spray 2010.**

# Sativex

## Clinical Efficacy

# Sativex: clinical experience

To date, the clinical program has involved over 1500 patients with MS. Over 1200 patient years of clinical experience with Sativex has been accumulated during the course of these clinical trials with more than >660 patients treated continuously for six months or more. In addition, there is over 5500 years of post-marketing and “Named Patient” use of Sativex (2000 patients in the UK, 250 in Italy and 150 in Spain).

# Sativex: clinical trials' programme

Phase III Clinical Trials (large studies in patients)

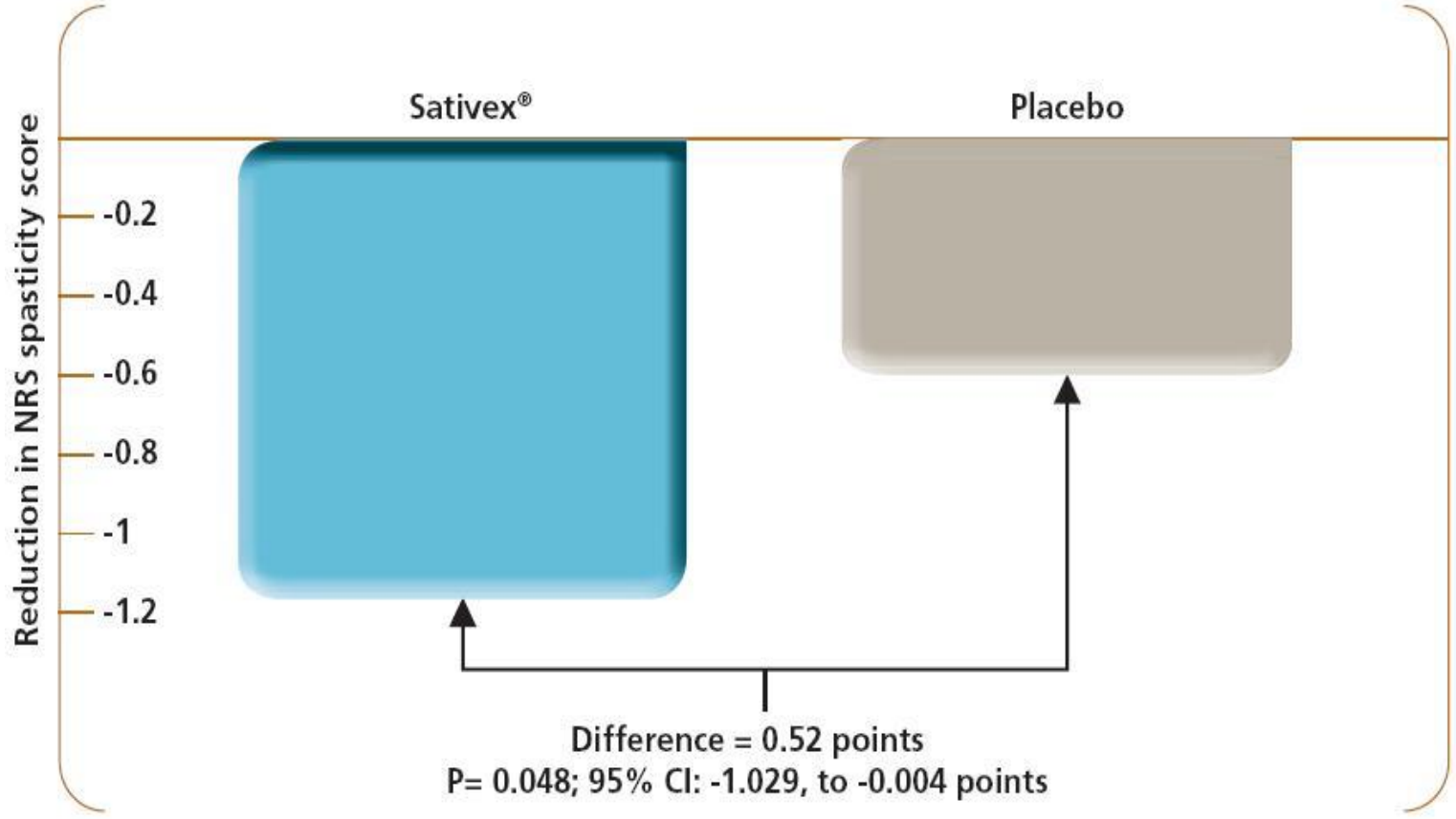
- 15 Phase III studies have been performed in large samples of patients with a variety of indications.
- 3 Clinical trials are considered pivotal for MS spasticity and 3 others are considered supportive for this indication (one pilot study, one long-term follow-up study and one withdrawal study).

# Sativex first pivotal clinical trial

| Status | Published |
|---|---|
| Location (s) | UK and Romania |
| Design | A Randomised, parallel group, double-blind, placebo-controlled study |
| Objective | To asses the efficacy and safety of Sativex vs. placebo in patients with MS spasticity |
| Participants and schedule | • n = 189 MS adult patients<br>• MS spasticity in 2 muscle groups and inadequate response to drug therapy<br>• Randomised to Sativex or placebo for 6 weeks<br>• Participants continued with current therapies throughout the study |
| Follow-up | 7-10 days follow up after active treatment period of 6 weeks |
| Primary outcome | Change in severity of spasticity using a daily patient-recorded numerical rating scale (NRS) |
| Secondary outcomes | • Ashworth scale of spasticity<br>• Motricity index<br>• Daily mean spasm scores<br>• Patient's global impression of change (PGIC) |

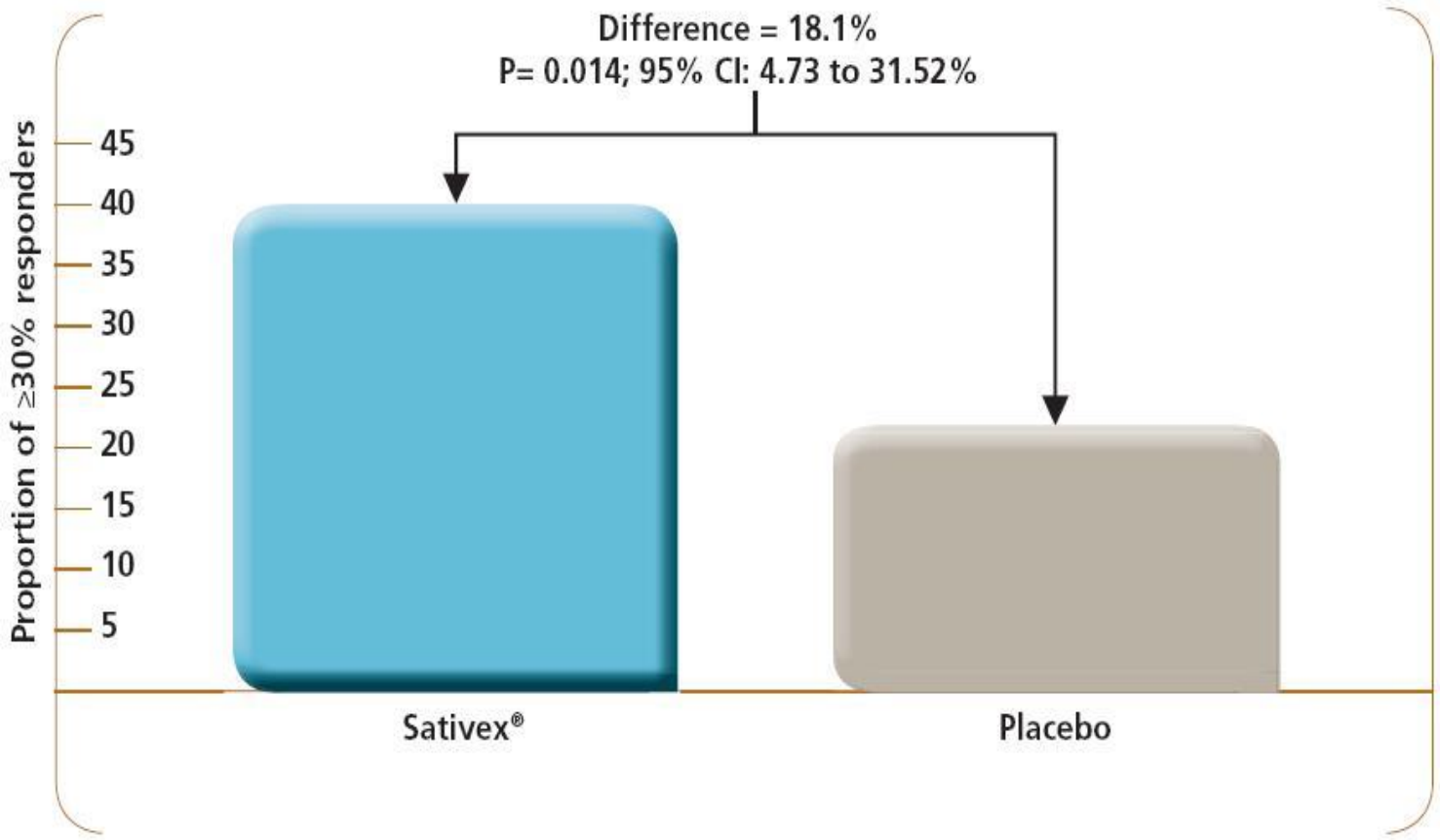
**Collin C et al. *Eur J Neurol* 2007; 14: 290-96.**

# Sativex first pivotal clinical trial results: patients spasticity NRS resolution




Collin et al.*Eur J Neurol* 2007; 14: 290- 96.

# Sativex first pivotal clinical trial results: patients improving ≥ 30% from baseline



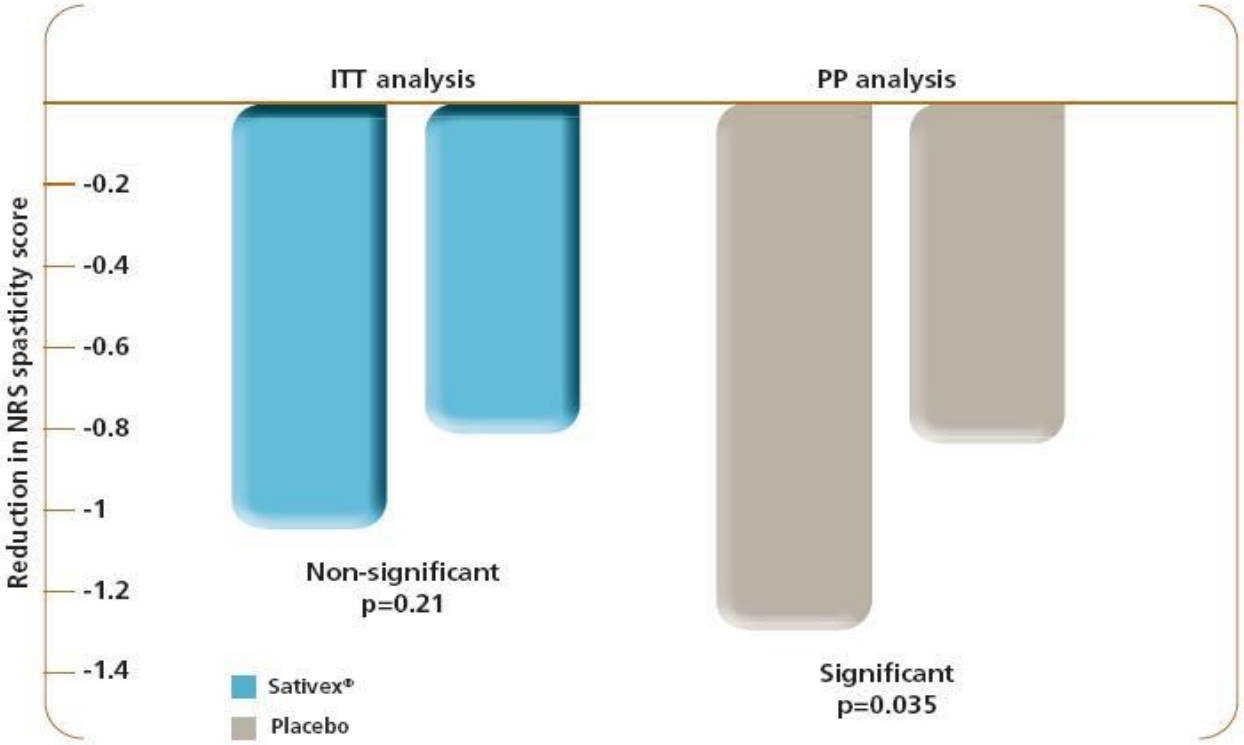

Collin et al.*Eur J Neurol* 2007; 14: 290- 96.

# Sativex second pivotal clinical trial

| Status | Published |
|---|---|
| Location | EU (multicentre) |
| Design | Randomised, placebo-controlled, double-blind, parallel group study |
| Objective | To assess the efficacy and safety of Sativex vs. placebo in patients with MS spasticity |
| Participants and schedule | • N = 337 MS adult patients<br>• MS with spasticity and an inadequate response to drug therapy<br>• 7-day baseline period then randomised to Sativex or placebo for14 weeks<br>• Participants continued with current therapies throughout the study |
| Follow-up | • 14 day follow-up after active treatment period of 14 weeks<br>• Visits after weeks 2,6,10 and at the end of the study (week 14 or on withdrawal) |
| Primary outcome | Change in Spasticity numerical rating scale (NRS) score |
| Secondary outcomes | • Modified Ashworth scale of spasticity<br>• Timed 10-metre walk<br>• Barthel ADL index<br>• Carer's global impression of change (CGIC)<br>• Quality of Life and others<br>• Safety and tolerability |

**Collin et al. *Neurol Res 2010***

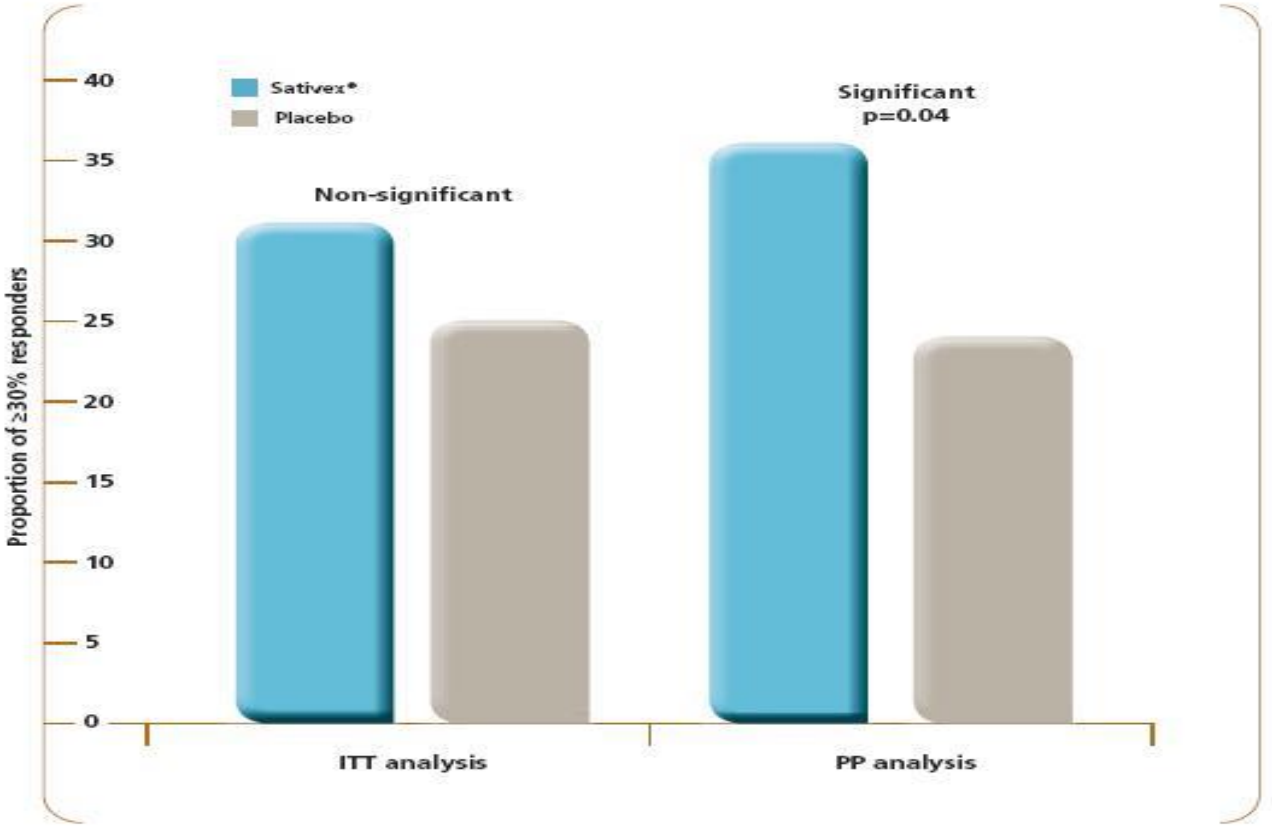
# Sativex second pivotal clinical trial results: patients spasticity NRS resolution




**ITT = intention-to-treat population**
**PP = per-protocol population**

**Collin et al. *Neurol Res* 2010.**

# Sativex second pivotal clinical trial results: patients improving ≥ 30% from baseline




**ITT = intention-to-treat population**
**PP = per-protocol population**

**Collin et al. *Neurol Res* 2010.**

# Sativex second pivotal clinical trial results: secondary outcomes

| Outcome | Adjusted mean change from baseline | | | | |
|---|---|---|---|---|---|
| | Population | Sativex | Placebo | Mean difference | P-value |
| NRS (proportion responders) | ITT | 0.31 | 0.25 | 0.059 | 0.231 |
| NRS (proportion responders) | PP | 0.36 | 0.24 | 0.116 | 0.04 |
| Median timed 10-m walk | ITT | -1.0 | -0.5 | 0.0 | 0.624 |
| Median timed 10-m walk | PP | -2.0 | 0.0 | -1.0 | 0.042 |
| Carer's global impression of change | ITT | Odds ratio = 1.25 (P = 0.270) (ease of transfer odds ratio = 1.578; p = 0.066) | | | |
| Carer's global impression of change | PP | Odds ratio = 1.79 (P = 0.013) (ease of transfer odds ratio = 2.144; p = 0.007) | | | |

**Collin et al. *Neurol Res* 2010.**

# Sativex second pivotal clinical trial results: other symptoms

Proportion of patients who achieved ≥30% improvement in 0-10 NRS score for other symptoms with Sativex:

- Fatigue 51%
- Spasm 76%
- Bladder 73%
- Tremor 80%
- Pain 76%
- Sleep 61%

Collin et al. *Neurol Res* 2010.

# Pooled-analysis of first 2 pivotal clinical trials with Sativex in patients with MS spasticity (n=526)

| Parameter | Difference between SAT and PL | Odds ratio | 95% CIs | p-value |
|---|---|---|---|---|
| Change in NRS spasticity score, PP population | -0.34 | NA | -0.64, -0.04 | 0.027 |
| Change in NRS spasticity score, modified ITT population | -0.40 | NA | -0.10, -0.007 | 0.0084 |
| CGIC, PP population | NA | 1.55 | 1.07, 2.25 | 0.027 |
| CGIC, modified ITT population | NA | 1.61 | 1.10, 2.35 | 0.017 |
| Pts achieving ≥ 30% reduction in NRS spasticity scores | 35% versus 24% | 1.63 | NA | 0.019 |

*Abbreviations:* CGIC, carer global impression of change; CIs, confidence intervals; ITT, intention-to-treat population; NA, not available/not applicable; NRS, numerical rating scale; PL, placebo; PP, per-protocol population; PL, placebo; SAT, Sativex.

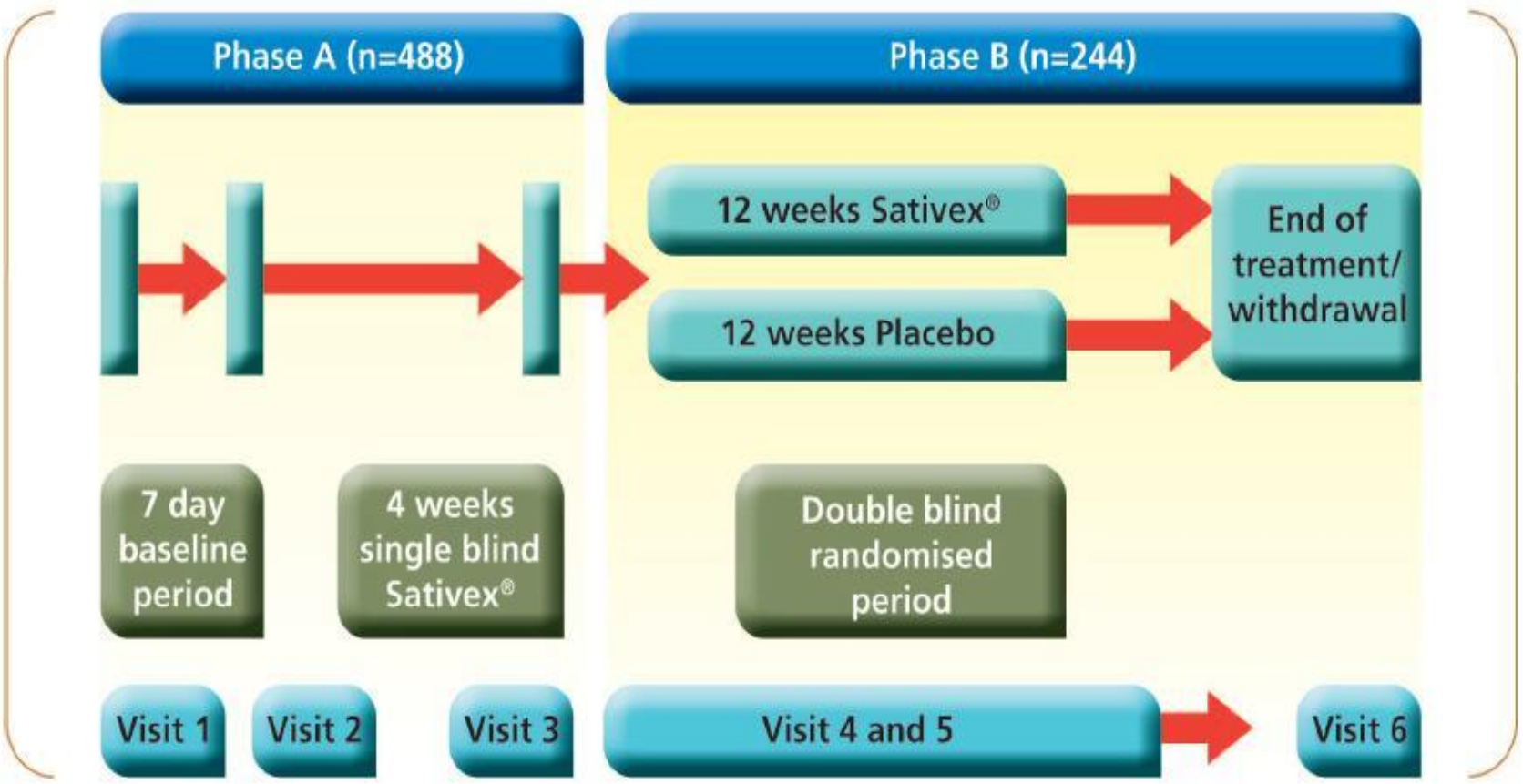
**Collin & Duncombe. *Mult Scler* 2006; 12: S13.**

# Sativex third pivotal clinical trial

| Status | Published (abstract available and full text pending) |
|---|---|
| Location | EU (multicentre) |
| Design | A 2-phase study: Phase A- single- blind response assessment and Phase B- a randomised, placebo-controlled, double-blind, parallel group study |
| Objective | To assess the efficacy and safety of Sativex vs. placebo in patients with MS spasticity |
| Participants and schedule | • N = 572 MS adult patients<br>• MS with spasticity and an inadequate response to drug therapy<br>• Single-blind Sativex for 4 week, with initial responders (improving 20% or more from baseline NRS score) randomised to Sativex or placebo for 12 more weeks<br>• Participants continued with current therapies throughout the study |
| Follow-up | •14 day follow-up after controlled period of 12 weeks |
| Primary outcome | Change in Spasticity numerical rating scale (NRS) score |
| Secondary outcomes | • Improvement in NRS responses of 30% or more and 50% or more<br>• Modified Ashworth scale of spasticity<br>• Timed 10-metre walk and motricity index<br>• Spasm frequency and sleep disruption<br>• Barthel ADL index<br>• Carer's global impression of change (CGIC)<br>• Quality of Life |

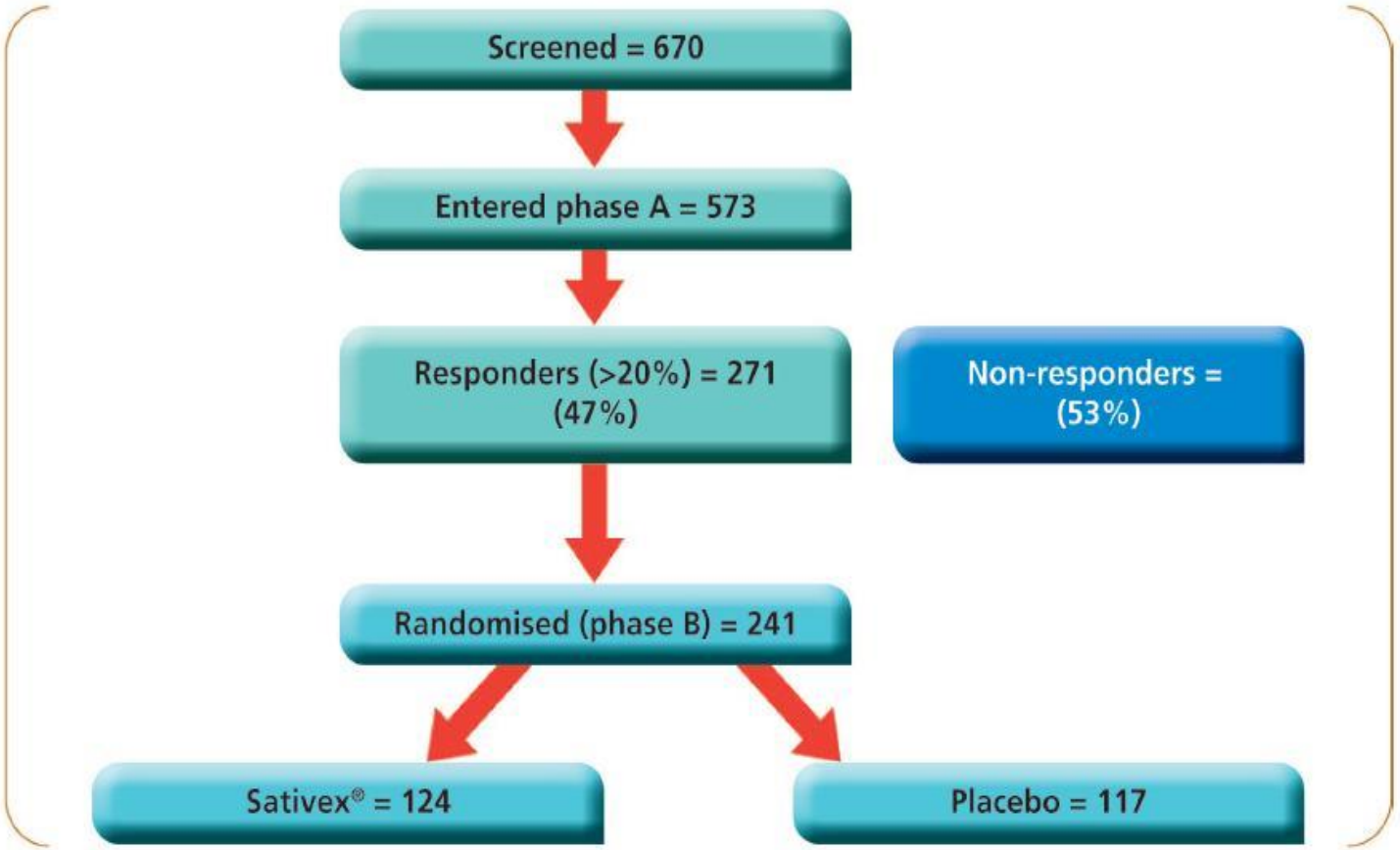
**Ambler et al. *Mult Scler* 2009; 15: S258.**

# Sativex third pivotal clinical trial: two-phase study design



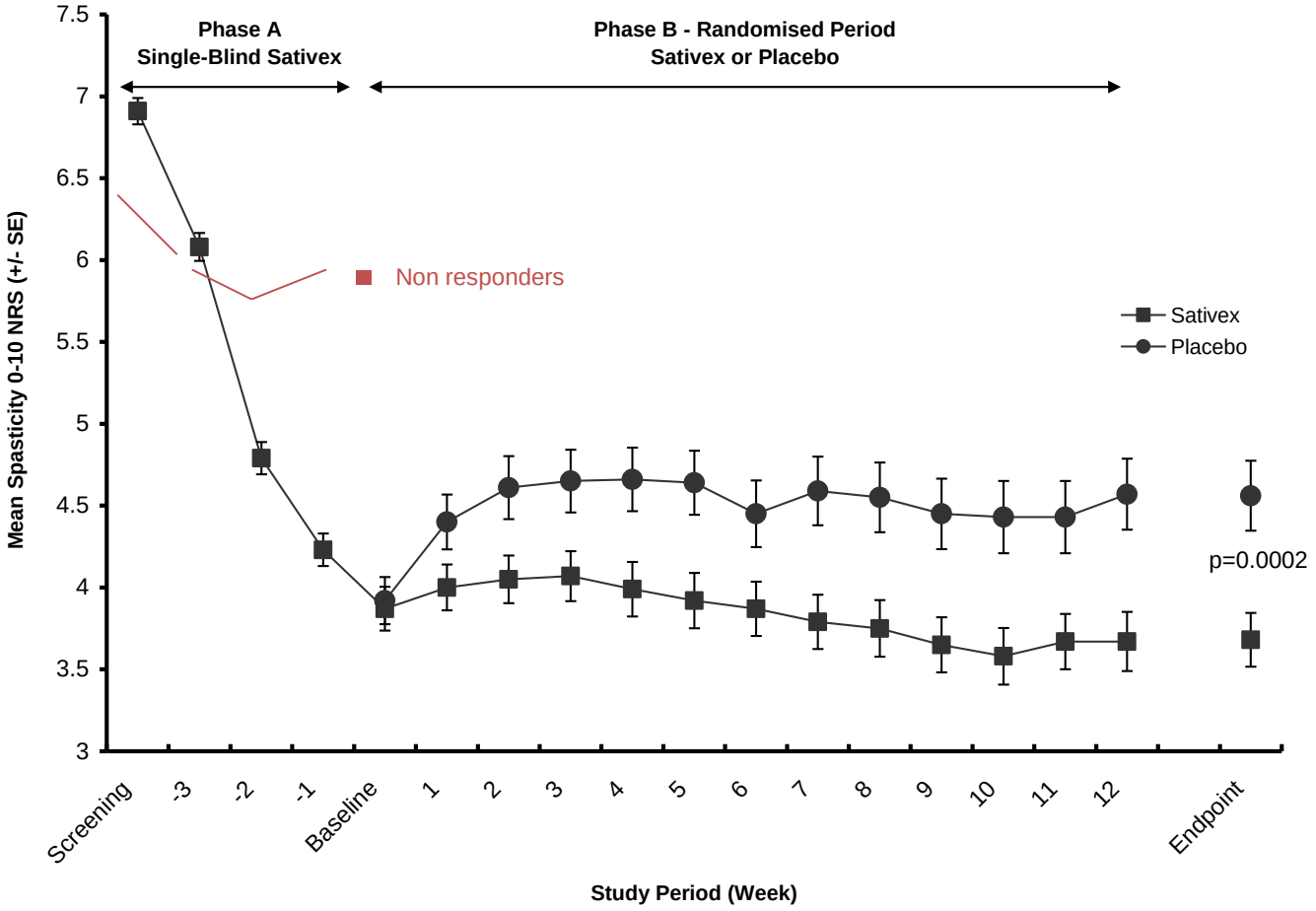

Ambler et al. *Mult Scler* 2009; 15: S258.

# Sativex third pivotal clinical trial: patient numbers



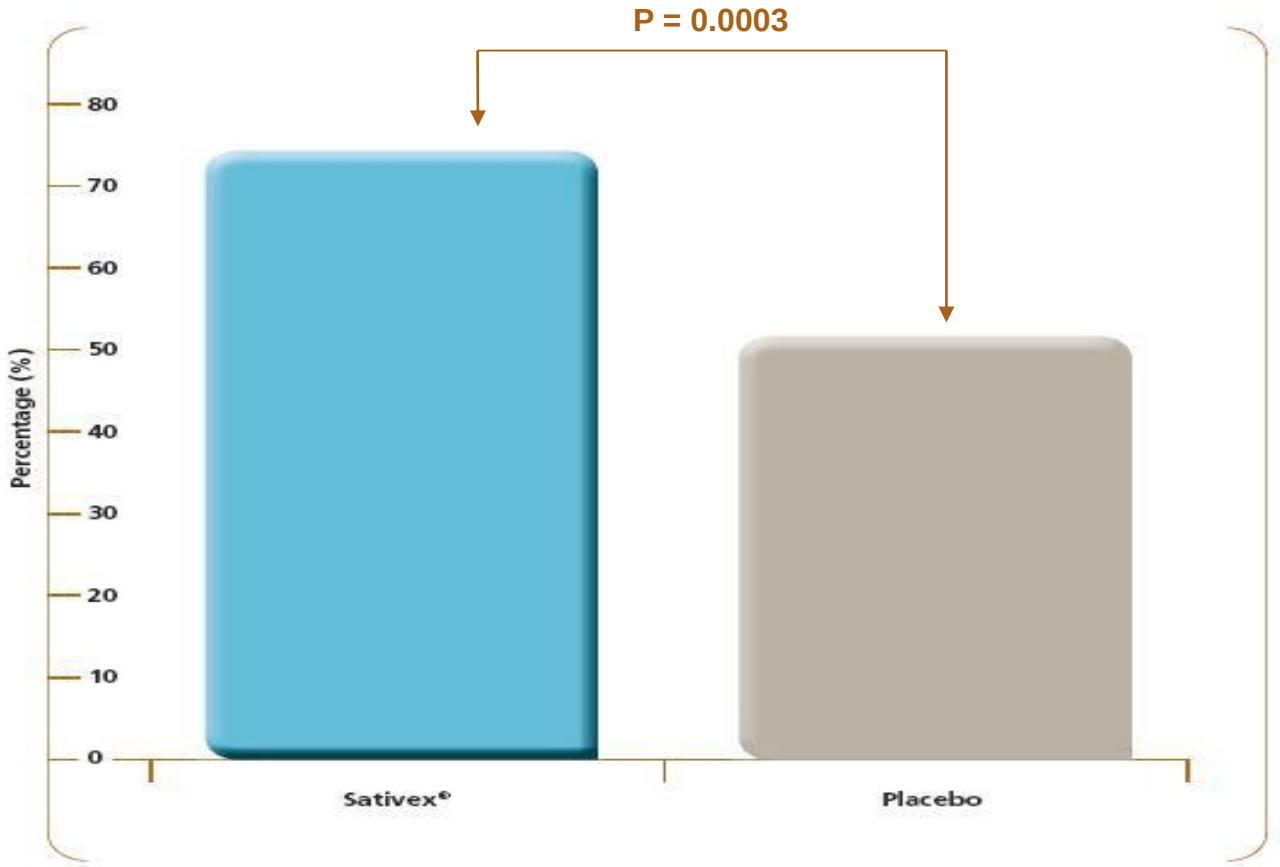

Ambler et al. *Mult Scler* 2009; 15: S258.

# Sativex third pivotal clinical trial results: NRS resolution from phase A re




Ambler et al. *Mult Scler* 2009; 15: S258.

# Sativex third pivotal clinical trial results: patients improving ≥ 30% from baseline at the 4th week




Ambler et al. *Mult Scler* 2009; 15: S258.

# Sativex third pivotal clinical trial results: patient well-being and quality of life (QoL)

Many measures of patient satisfaction and factors associated with QoL and overall well-being were improved in the Sativex third pivotal clinical trial:

- Barthel activities of daily living (ADL) ($p = 0.0067$).
- Physician, carer and patient global impression of change ($p = 0.0045$, $p = 0.0053$ and $p = 0.0234$, respectively).
- Sleep disruption NRS ($p < 0.0001$).
- Spasm frequency ($p = 0.0046$).
- QoL EQ-5D (0.48 to 0.57; +19%).
- QoL SF-36 Role Physical 0-100 (35.1 to 48.1; +37%).

**Ambler et al. *Mult Scler* 2009; 15: S258; Montalbán & Wright *Mult Scler* 2009; 15: S272.**

# Sativex long-term follow-up clinical trial

| Status | Published |
|---|---|
| Location | UK |
| Design | Long-term follow-up of the randomised, double-blind, pilot trial |
| Objective | To monitor the safety and efficacy of Sativex during long-term use in patients with MS-spasticity |
| Participants and schedule | • N = 137 MS adult patients<br>• MS with one or more prominent symptoms: spasticity, spasms, bladder problems, tremor or pain and who completed the pilot study<br>• After 1-year, participants (n = 25) stopped Sativex suddenly for a maximum of 14 days |
| Additional study details | • 137 eligible patients were assessed every 8 weeks using VAS and followed for a mean of 434 days (range 21 to 814 days). A total of 58 patients withdrew for reasons including lack of efficacy and AEs. 25 patients agreed to stop therapy to assess if withdrawal symptoms occurred |
| Follow-up | Median follow-up to date 735 days (range 1 to 1,149 days); 14-day withdrawal sub-study |
| Primary outcome | Severity of most troubling symptom using the visual analogue scale (VAS) |
| Secondary outcomes | • Severity of other symptoms (VAS) |

**Wade et al. *Mult Scler* 2006; 12: 639-45.**

# Sativex long-term follow-up clinical trial results

- For patients who remained in the study for at least 1 year symptom scores remained significantly lower with Sativex than baseline values. For example: spasticity (69.5, 34.2 and 31.8 at 0, 10 and 82 weeks, respectively).
- 25 patients interrupted treatment for 2 weeks and 20% needed to resume Sativex before the end of 14 days due to re-emergence of marked symptoms.
- During the interruption period 7 patients reported that their MS symptoms were much worse, 10 said that they were worse, 5 the same and 3 reported an improvement in symptoms.

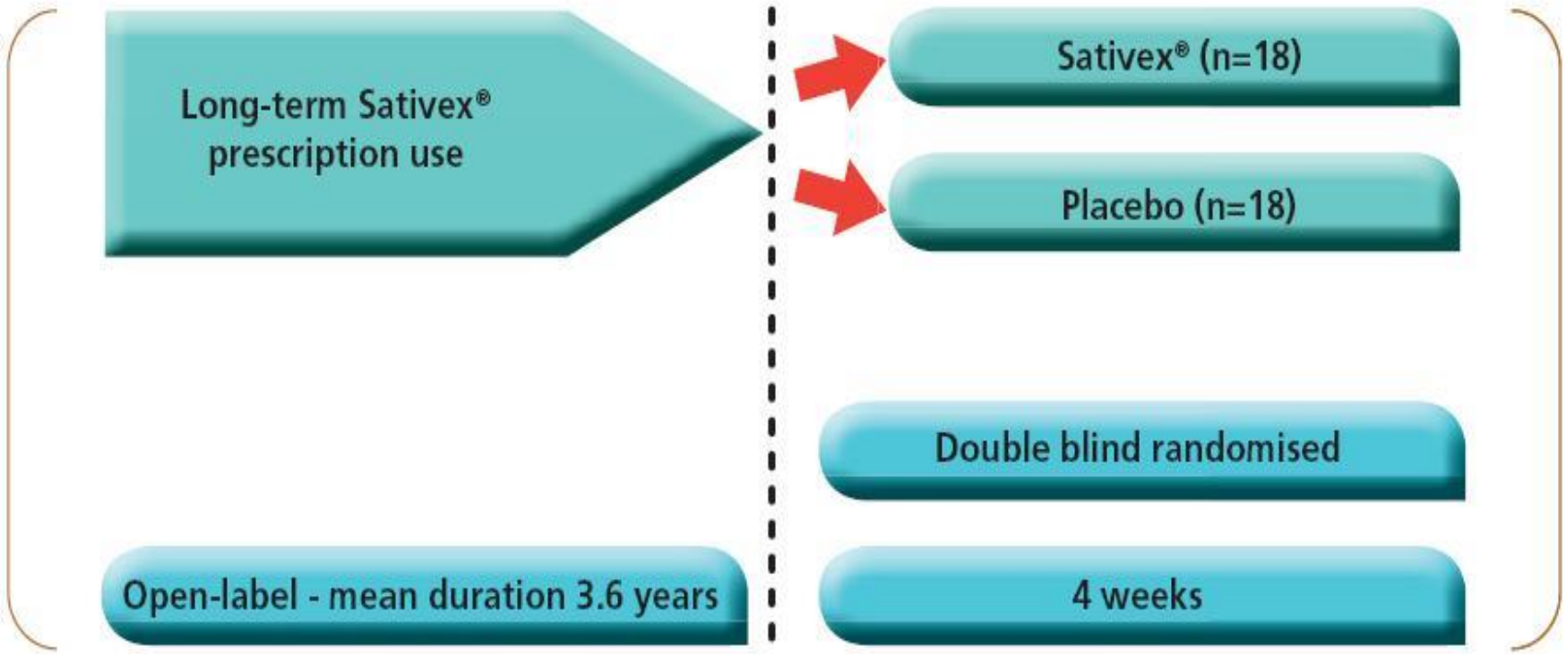
**Wade et al. *Mult Scler* 2006; 12: 639-45.**

# Sativex withdrawal clinical trial

| Status | Published (abstract available and full text pending) |
|---|---|
| Location | UK |
| Design | A randomised, placebo-controlled, parallel group withdrawal study |
| Objective | To assess the maintenance of efficacy after long-term treatment of MS spasticity with Sativex |
| Participants and schedule | • N = 36 MS adult patients<br>• MS with spasticity and treated with Sativex for at least 12 weeks<br>• One week baseline on Sativex, then randomised to Sativex or placebo for 4 weeks<br>• Participants continued with current therapies throughout the study |
| Follow-up | • 4 weeks controlled withdrawal period |
| Primary outcome | Time to treatment failure |
| Secondary outcomes | • Severity of spasticity<br>• Sleep disruption (NRS)<br>• Modified Ashworth scale<br>• Timed 10-metre walk<br>• Motricity index<br>• Spasm frequency and<br>• Barthel ADL index<br>• Carer's global impression of change (CGIC)<br>• Patient's global impression of change (PGIC) |

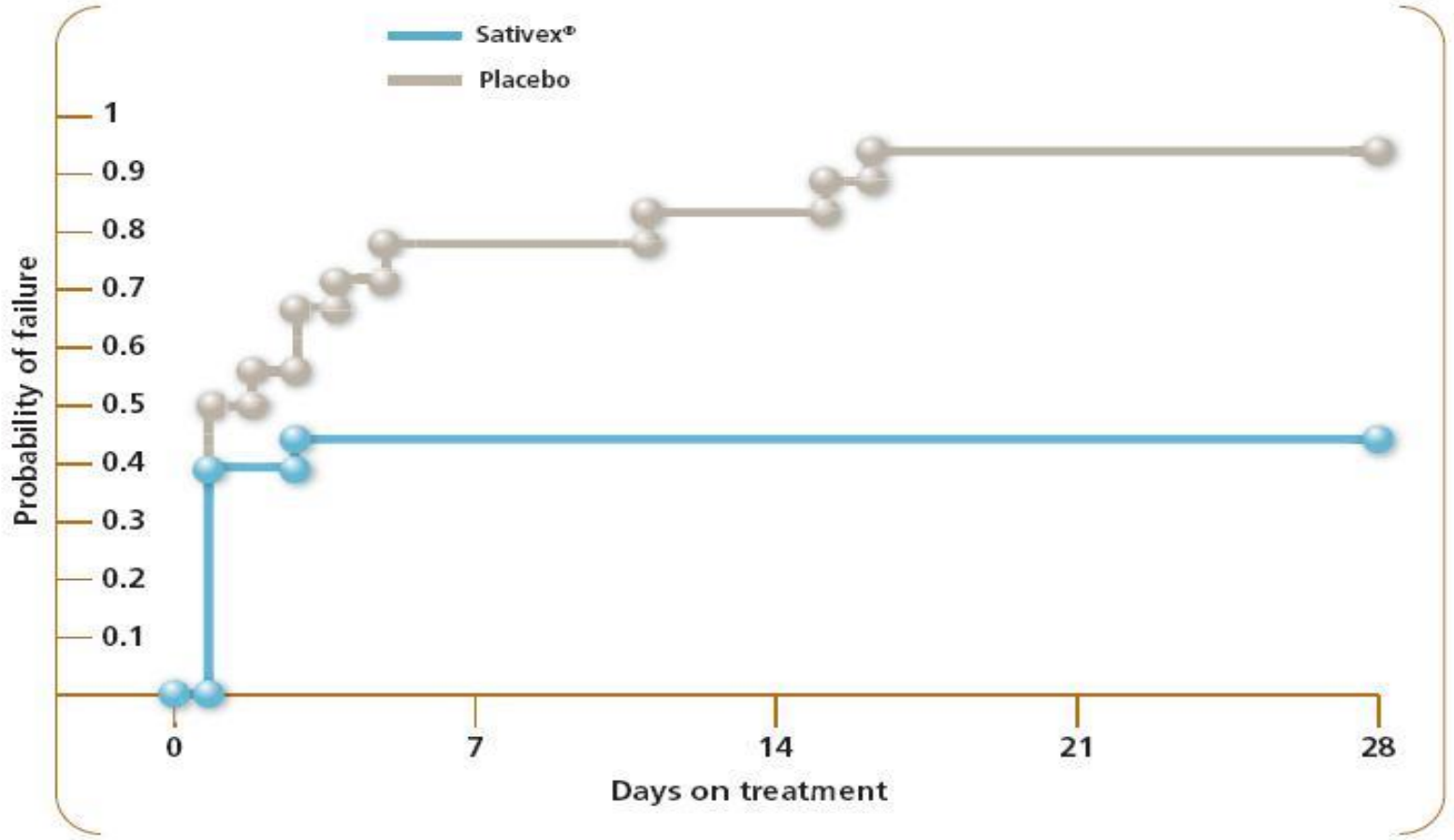
**Notcutt et al. *Mult Scler* 2009; 15: S258**

# Sativex withdrawal clinical trial: study structure




Notcutt et al. *Mult Scler* 2009; 15: S258

# Sativex withdrawal clinical trial: patient evolution




Notcutt et al. *Mult Scler* 2009; 15: S258.

# Sativex

## Clinical Tolerability and Safety

# Sativex: adverse events (AEs)

- During the first 4 weeks of exposure dizziness (14-32%) and fatigue (12-25%) were the most common AEs.
- Usually mild to moderate and resolved quickly.
- When the recommended gradual “up titration” schedule was introduced the incidence of AEs was reduced.
- In clinical trials the rates of withdrawal due to AEs was low.
- Sativex does not exhibit the side effects typically associated with recreational cannabis use.

**Wade et al. *Mult Scler* 2004; 10: 434-41; Wade et al. *Mult Scler* 2006; 12: 639-45; Collin et al. *Eur J Neurol* 2007; 14:290-96. Collin et al. *Mult Scler* 2007; 13: S129; Ambler et al. *Mult Scler* 2009; 15: S258.**

# Sativex AEs listed in the SmPC

| MeDRa System Organ Class disorders | Very common ≥1/10 | Common ≥1/100 to <1/10 | Uncommon ≥1/1000 to <1/100 |
|---|---|---|---|
| Infections and infestations | | | Pharyngitis |
| Metabolism and nutrition | | Anorexia (including ↓appetite), ↑ appetite | |
| Psychiatric | | Depression, disorientation, dissociation, euphoria | Hallucinations, illusions, paranoia, suicidal ideation, delusional perception |
| Nervous system | Dizziness | Amnesia, balance disorder, attention problems, memory impairment, somnolence, dysarthria, dysgeusia, lethargy | Syncope |
| Eye | | Blurred vision | |
| Ear and labyrinth | | Vertigo | |
| Cardiac | | | Palpitations, tachycardia |
| Vascular | | | Hypertension |
| Respiratory, thoracic , mediastinal | | | Throat irritation |
| Gastrointestinal | | Constipation, diarrhoea, nausea, dry mouth, glossodynia, vomiting, mouth ulcers, oral discomfort/pain, | Abdominal pain, oral mucosal discolouration/disorders/exfoliation, stomatitis, tooth discolour |
| General disrders and admin site | Fatigue | Application site pain, asthenia, feeling abnormal/drunk, malaise | Application site irritation |
| Injury. Poisoning and procedural | | fall | |

# Treatment-related neurological AEs

[From Sativex integrated safety analysis (Sept 1, 2007) from non-cancer studies]

| Preferred Term | Sativex (n = 921) | Placebo (n = 853) |
|---|---|---|
| Disturbance in attention | 37 (4%) | 2 (0.2%) |
| Memory impairment | 14 (1.5%) | 4 (0.5%) |
| Amnesia | 9 (1%) | 1 (0.1%) |
| Coordination abnormal | 5 (0.5%) | 0 |
| Cognitive disorder | 2 (0.2%) | 0 |
| Depressed consciousness | 2 (0.2%) | 0 |

**NB. These data do not include results from the third pivotal clinical trial which used the "up-titration" schedule and was associated with a significantly lower incidence of AEs.**

**[From Sativex integrated safety analysis (Sept 1, 2007) from non-cancer studies.]**

# 10 Most frequent treatment-related psychiatric AEs with Sativex

| Event | Sativex MS N = 496 | Placebo MS N = 434 |
|---|---|---|
| Disorientation | 27 (5.4%) | 4 (0.9%) |
| Dissociation | 14 (2.8%) | 1 (0.2%) |
| Euphoric mood | 12 (2.4%) | 6 (1.4%) |
| Depressed Mood | 7 (1.4%) | 1 (0.2%) |
| Confusional State | 5 (1.0%) | 0 |
| Depression | 5 (1.0%) | 1 (0.2%) |
| Hallucination | 5 (1.0%) | 1 (0.2%) |
| Apathy | 4 (0.8%) | 1 (0.2%) |
| Paranoia | 4 (0.8%) | 1 (0.2%) |
| Anxiety | 3 (0.6%) | 5 (1.2%) |

NB. These data do not include results from the third pivotal clinical trial which used the “up-titration” schedule and was associated with a significantly lower incidence of AEs.

[From Sativex integrated safety analysis (May 11, 2007)]

# Cognitive and Neuropsychiatric Effects

- Cognitive impairment occurs with Sativex, but in the majority of instances the symptoms were mild-to-moderate.
- Psychiatric AEs were also reported for Sativex , but they were mostly of mild-to-moderate severity.
- There is no evidence from RCTs that Sativex poses any long-term or irreversible neuropsychiatric or cognitive risk to patients

**[From Sativex integrated safety analysis (May 11, 2007)]**

# Potencial for abuse

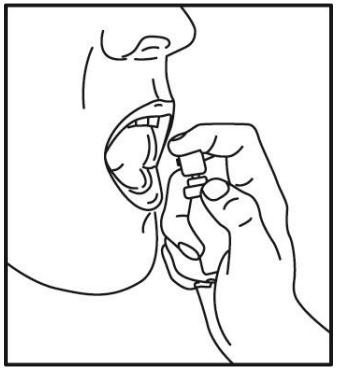
- Sativex does not exhibit the psychostimulant effects typically associated with recreational cannabis use.
- Intoxication was reported to be very low during the course of short- and long-term studies.
- Sativex has not been associated with signs of drug tolerance and in a long-term trial the mean dosage decreased slightly.
- No consistent withdrawal syndrome has been observed, and there is no evidence of drug misuse or abuse.
- Sativex was shown to have lower abuse potential than equivalent doses of dronabinol, which itself is considered to have minimal abuse potential, in 23 abuse-prone recreational marijuana users.

Wade et al. *Mult Scler* 2006;12: 639-45; Collin et al. *Eur J Neurol* 2007; 14:290-96; Schoedel et al. 2010.

# Clinical safety conclusions

- AEs with Sativex during the early stages of treatment are common, but they are generally mild-to-moderate in severity and rarely require treatment to be discontinued.
- Dizziness and fatigue are the 2 most common AEs.
- Introduction of a gradual “up titration” schedule markedly reduced the incidence of AEs.
- Sativex is not associated with the side effects that typically occur with street cannabis.

# Sativex administration



- Sativex is for oromucosal delivery only.
- The spray should be directed to different sites on the oromucosal surface (inside the cheek or under the tongue) each time it is used.
- The “up titration” schedule is recommended to achieve the optimal dosage up to maximum of 12 sprays/day. **(Average number of sprays in clinical trials was 8 sprays/day)**
- If a dose is forgotten, then a spray should be administered as soon as the patient remembers or when required.
- The patient must not administer 2 sprays at the same time to make up for a missed dose.

# Overall Conclusions (1/2)

- Results from controlled RCTs provide conclusive evidence of the short and long term efficacy of Sativex in MS-related spasticity. Half of patients benefit clearly of this add-on treatment
- The responders selection can be done after 4 weeks of treatment
- The treatment has also shown improvements in MS spasticity associated symptoms, such as spasms or sleep disruptions, and functional status and QoL

# Overall Conclusions (2/2)

- Mild to moderate dizziness and fatigue are the most common AEs, which can be reduced with careful dose titration schedule
- The medication does not appear to pose safety or long term concerns: it has not been associated with drug tolerance signs or with withdrawal syndrome, and there has been no evidence of drug misuse or abuse.

**This THC:CBD oromucosal spray appears as a solid and welcomed option for resistant spasticity in MS patients**