THC/CBD and CBD in Spasticity and Epilepsy Regulatory Trials

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Almirall Global Medical Affairs

- Swiss Task Force for Cannabinoids in Medicine (STCM)
- Swiss Academy of Pharmaceutical Sciences (SAPhS)
- 2016 Conference
- Cannabinoids in Medicine – New Trends
- Saturday Nov the 12th 2016,
- Bern Inselspital - University Hospital
1. Rationale for developing THC/CBD oromucosal spray
2. Pre-clinical programs
3. Clinical Trial Programs: Efficacy and Tolerability
4. Observational studies
5. CBD in Epilepsy
6. Conclusions
Rationale for the development of Sativex®, THC/CBD 1:1 ratio oromucosal spray

- Smoked cannabis has variable pharmacokinetics, causing very high THC peaks, which lead to psychoactivity and other adverse events\(^1\)

- In recent herbal samples high levels of THC (psychoactive cannabinoid) and low levels of CBD (antipsychotic cannabinoid) were reported\(^2\)

- Street cannabis lacks standardization and purity and there legal issues regarding its use\(^3\)

- Smoked cannabis increases the risk of lung cancer, heart disease, etc.\(^4\)

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Rationale for the development of Sativex®, THC/CBD 1:1 ratio oromucosal spray

- To produce a standardised medicinal product based upon the main active constituents of *Cannabis sativa*, tetrahydrocannabinol (THC) and cannabidiol (CBD)\(^1\)
- Formulated to ensure purity and stability \(^2\)
- To administer in a way (oromucosal) which provides a satisfactory pharmacokinetic profile avoiding the high plasma levels and risks associated with smoking \(^3\)
- To benefit from the synergistic interaction between CBD and THC, with a reduction in psychoactivity and enhanced cannabinoid-mediated clinical effects \(^4\)

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Sativex®: definition and origin

- Sativex® is an endocannabinoid system modulator. The endocannabinoid system is involved in the muscle tone control and is affected in MS.

- It is a unique cannabinoid-based medicine derived from the active principles of Cannabis sativa plant, THC and CBD.

- The pharmaceutical form is prepared from 2 cloned chemovars of C. sativa plant 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.

1. Perez Drugs of Today 2006; 42: 495-501
2. SmPC Sativex® Oromucosal Spray February 2014.
Sativex® is indicated as treatment for symptom improvement in adult patients with moderate to severe spasticity due to multiple sclerosis (MS) who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy.
Endocannabinoids in Sativex®: mechanism of action

- Sativex® principally contains two cannabinoids, 9-delta-tetrahydrocannabinol (THC) and cannabidiol (CBD)\(^1\)

- THC and CBD act upon the human cannabinoid receptors $\text{CB}_1$ and $\text{CB}_2$ (G protein-coupled receptors) which are involved in different pathways, such as the transmission of nerve impulses $^{1,2}$

- $\text{CB}_1$ receptors are found predominantly at central and peripheral nerve terminals, while $\text{CB}_2$ receptors occur mainly on immune cells $^2$

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1. Perez Drugs of Today 2006; 42: 495-501
2. Pertwee Br J Pharmacol 2006; 147: S163-71
Endocannabinoids: mechanism of action

THC and CBD: synergy at Sativex® dose levels (complementary effects)

THC
- Antiemetic
- Muscle relaxation
- Appetite stimulation
- Psychoactive

CBD
- Analgesic
- Anti-convulsant
- Anxiolytic
- Neuroprotective

Pre-Clinical Safety Program
– for all cannabinoid compounds

• Full pre-clinical safety program completed, including
  1. Reproductive toxicology
  2. Safety Pharmacology studies
     1. Cardiovascular
     2. Central Nervous System
     3. Respiratory
  3. Genotoxicology – in vivo and in vitro
  4. Acute and chronic repeat dose toxicology
     1. Including 6 month rat and 12 month dog studies
  5. Local Irritation Studies (Sativex only)
  6. Cytochrome P450 inhibition/induction studies
  7. PgP and other transporter inhibition studies
  8. Immunotoxicology
  9. Rodent abuse liability studies
  10. Carcinogenicity studies

• No unexpected safety issues identified during pre-clinical safety studies
## Evidence Base from placebo-controlled clinical trials - Sativex

<table>
<thead>
<tr>
<th>Phase</th>
<th>Title</th>
<th>Key Result</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Supportive Studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase II</td>
<td>Symptoms of MS and other nervous system conditions (n=25, Wade 2003)</td>
<td>Spasticity</td>
<td>p=0.042</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Spasm, Sleep</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Phase III</td>
<td>GWMS001: MS symptoms (n=160, Wade 2004)</td>
<td>Spasticity</td>
<td>p=0.001</td>
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<tr>
<td></td>
<td></td>
<td>Sleep</td>
<td>p=0.047</td>
</tr>
<tr>
<td><strong>Original Pivotal Studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase III</td>
<td>GWMS0106: Spasticity due to MS (n=189, Collin 2007)</td>
<td>Spasticity</td>
<td>p=0.047</td>
</tr>
<tr>
<td>Phase III</td>
<td>GWCL0403: Spasticity due to MS (n=337, Collin 2010)</td>
<td>Spasticity</td>
<td>p&lt;0.05 (PP)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P = NS (ITT)</td>
</tr>
<tr>
<td><strong>Pooled Analysis</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Spasticity due to MS (n=666, Wade 2010)</td>
<td>Spasticity</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PGIC</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td><strong>3rd Pivotal Study Requested by MHRA</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Phase III</td>
<td>GWSP0604: Spasticity due to MS (n=571) (n=241 in Phase B, Novotna 2011)</td>
<td>Spasticity</td>
<td>p=0.0002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All key endpoints</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td><strong>Long term efficacy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GWSP0702: Spasticity due to MS (n=36, Notcutt 2013)</td>
<td>Spasticity, PGIC, CGIC</td>
<td>p=0.01: p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>GWMS1132: 12 month placebo-controlled (n=120, Vachova 2014)</td>
<td>Spasticity, cognition</td>
<td>P = 0.001</td>
</tr>
</tbody>
</table>
• Phase I Clinical Trials (studies in healthy subjects): PK, PD
• Phase II Clinical Trials: 8 Studies have been conducted to assess the safety and efficacy of Sativex® in patients with MS, spinal cord injury or various pain states
• **Main Phase III CTs: Main endpoint evolution: Statistically significant improvements vs. Placebo**
  - n= 160, 6 weeks. Wade et al. *Mult Scler* 2004;10: 434-41. MS Spasticity mean VAS scores were reduced by -31.2% vs. -8.4% with Placebo (p=0.001 ITT and PP)
  - n=189, 6 weeks. Collin et al. *Eur J Neurol* 2007; 14: 290-96. 0-10 NRS mean score evolution: -1.2 vs. 0.6 (p<0.05, ITT and PP)
  - n= 337, 14 weeks. Collin et al. *Neurol Res* 2010 Jun;32(5)451-9. 0-10 NRS mean score evolution: -1.2 vs. 0.8 (p<0.05, PP)
  - N=572, 4+12 weeks. Novotna et al. *Eur J Neurol* 2011 Sep;18(9): 1122-31. 0-10 NRS mean score evolution: Over -3 in the enrichment phase: -0.04 vs. (p<0.05, ITT and PP)
Sativex® first pivotal clinical trial results (1/2)

- Patients’ MS spasticity 0-10 NRS mean score evolution (n=189)
  Good results in average, and more effective than placebo

- Difference = 0.52 points
  \[ p = 0.048; \text{95\% CI:} -1.029 \text{ to } -0.004 \]

3 Sativex® second pivotal clinical trial results

- **36%** of previously resistant patients improved ≥ 30% their 0-10 MSS NRS score from baseline (clinically relevant improvement) % of patients with high improvements in MSS associated symptoms (≥ 30%) within the MSS NRS responders patient pool:

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>51%</td>
</tr>
<tr>
<td>Spasms</td>
<td>76%</td>
</tr>
<tr>
<td>Bladder</td>
<td>73%</td>
</tr>
<tr>
<td>Tremor</td>
<td>80%</td>
</tr>
<tr>
<td>Pain</td>
<td>76%</td>
</tr>
<tr>
<td>Sleep</td>
<td>61%</td>
</tr>
</tbody>
</table>

Sativex® third pivotal clinical trial (1/6)

- Two-phase study design → Phase A: Enrichment to detect Sativex® early responders,¹ Phase B: Randomized vs. Placebo ²

Initial responders identification

- A 4 weeks’ trial period, where all participants were to receive Sativex® (single blind manner), was implemented. ¹

- Patients improving their baseline 0-10 NRS MSS scores ≥20% after the 4 weeks trial period were labelled “initial responders”, and were allowed to go on into the study second phase, randomized to placebo in a double blind manner ¹, ²

- The 20% threshold at 4 weeks was chosen as a predictor of final achievement of a clinically relevant response (≥30% 0-10 NRS score improvement vs. baseline) ¹, ²

Sativex® third pivotal clinical trial (3/6)
Patients’ disposition

- 47% of patients were initial responders

Screened = 670

Entered phase A = 573

Responders (>20%) = 271 (47%)
Non-responders = (53%)

Randomised (phase B) = 241

Sativex® = 124
Placebo = 117

Sativex® third pivotal clinical trial results (4/6)

- NRS evolution after randomization:
  Sativex® effect maintained, whereas placebo allocated patients worsened

Sativex®: clinical trials’ program

• Phase IV study Clinical Trial
  Cognition and mood: Randomized and placebo controlled long term follow-up clinical trial
  
  – n=120, 50 weeks
  – 0-120 PASAT score evolution: + 6.8 in both groups (not significantly differences).
  – Mood inventory: no statistically significant effect vs. Placebo
  – MS patients allocated to Sativex® improved their spasticity more than the placebo allocated ones following the patient, carer and clinician's evaluations.

Vachova et al, J Mult Scler 2014 1:2
Efficacy: Global impression of change (GIC) in spasticity over 50 weeks

7-point scale from “Very much worse” to “Very much better”

Patients, carers and physicians rated how spasticity had changed since Visit 1

Vachova et al, J Mult Scler 2014 1:2

*** p<0.001; ** p=0.0014; * p=0.0042
Sativex® Clinical Trials Efficacy: Conclusions

- Results from well-controlled RCTs provide conclusive evidence of the efficacy of Sativex® in reducing the severity of MS-related spasticity.
- The proportion of patients showing a 30% or greater improvement in spasticity symptoms (clinically relevant effect) was significantly higher with Sativex® than with placebo in previously resistant to MSS treatment patients.
- Randomized withdrawal of Sativex® treatment provided definitive proof of efficacy since stopping treatment precipitated significant worsening of spasticity.
- Long term cognition CT shows maintenance of effect after 1 year and absence of cognition and/or mood worsenings.
### Sativex® AEs listed in the SmPC

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

SmPC Sativex® Oromucosal Spray February 2014
Sativex®, lack of abuse potential

- 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.

3. SmPC Sativex® Oromucosal Spray February 2014
Sativex® spray: Long term follow-up: Cognition clinical trial
Tolerability during 50 weeks’ treatment\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>THC:CBD spray (n=62)</th>
<th>Placebo (n=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>39 (63%)</td>
<td>19 (32%)</td>
</tr>
<tr>
<td>Treatment-related</td>
<td>25 (40.3%)</td>
<td>5 (8.5%)</td>
</tr>
<tr>
<td>Vertigo</td>
<td>6 (9.7%)</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5 (8.1%)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5 (8.1%)</td>
<td>1 (1.7%)</td>
</tr>
<tr>
<td>Muscle spasticity</td>
<td>5 (8.1%)</td>
<td>2 (3.4%)</td>
</tr>
<tr>
<td>Respiratory tract infection</td>
<td>0</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Withdrawals from Study</td>
<td>12 (19%)</td>
<td>11 (19%)</td>
</tr>
<tr>
<td>AE</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Withdrew consent</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Investigator decision</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Vachova et al, J Mult Scler 2014 1:2
THC:CBD spray, Cognition Long Term clinical trial

- No effect on cognition or depression over 50 weeks \(^1\),
  - Mean dose 6.4 sprays/day \(^1\)
  - Cognition: no statistically significant effect compared with placebo \(^1\)
  - Beck Depression Inventory: no statistically significant effect vs. placebo \(^1\)

Vachova et al, J Mult Scler 2014 1:2
Sativex® in everyday clinical practice

Observational studies

1. MOVE 2 Germany observational study (n=355)
2. MOVE 2 Italy observational study (n=433)
3. UK survey on ADL (n=124)
4. UK Long term follow-up (n=146)
5. Driving ability study (n=33)
6. UK and Germany (and CH) Registries (n=941)
7. Spain Registry (n=205)
8. Italian Registry (n=1615)

• … 50 000 patient/years of exposure

5. Freidel et al.. Acta Neurol Scan 2015 Jan;131(1):9-16
6. Etges T et al, ECTRIMS Online Library. Etges T. Oct 9, 2015; 116002
8. Patti F. Et al. J Neurol Neurosurg Psychiatry. 2015 Sep;87(9):944-51
Sativex® use in clinical practice data:

• Short term effectiveness is aligned with the clinical trials data, improving 1/3 to 1/2 of previously resistant patients, including spasticity, associated symptoms and daily life improvements.

• Effectiveness is maintained in the long term.

• No new signals of tolerability or safety concerns. Adverse events mainly mild to moderate.

• No impairment of driving ability, cognition or mood.

• Sativex® shows to be a valid new option for undeserved moderate to severe MS Spasticity patients.
5 CBD (Epidiolex®) scientific rationale

CBD in animal models of seizures

**MES Model**

**Audiogenic Model**

**PTZ Model**

Jones et al., 2010. JPET 332: 567-577
Reverting Over-expressed Seizure Genes

- Genes dysregulated in patients/models revert to normal levels
  - Correlates with response

<table>
<thead>
<tr>
<th>Gene symbol</th>
<th>Gene Function Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPARC</td>
<td>Cell growth</td>
</tr>
<tr>
<td>A2M</td>
<td>Immune system</td>
</tr>
<tr>
<td>CCL3</td>
<td>Immune system</td>
</tr>
<tr>
<td>CCL4</td>
<td>Immune system</td>
</tr>
<tr>
<td>C3</td>
<td>Immune system</td>
</tr>
<tr>
<td>cFOS</td>
<td>Neuronal Firing</td>
</tr>
<tr>
<td>GFAP</td>
<td>Nervous system</td>
</tr>
<tr>
<td>KCNK1</td>
<td>Nervous system</td>
</tr>
<tr>
<td>PENK</td>
<td>Nervous system</td>
</tr>
<tr>
<td>NPY</td>
<td>Nervous system</td>
</tr>
<tr>
<td>ARC</td>
<td>Nervous system</td>
</tr>
<tr>
<td>CD9</td>
<td>Nervous system</td>
</tr>
<tr>
<td>BDNF</td>
<td>Nervous system development</td>
</tr>
<tr>
<td>EGR1</td>
<td>Stress response</td>
</tr>
</tbody>
</table>

**mRNA Expression (fold change from control)**

- **cFos** (neuronal activity)
  - Vehicle + Saline
  - Vehicle + PTZ: P=0.1089
  - CBDV + Saline: P=0.0045
  - CBDV + PTZ

- **EGR1** (marker of stress)
  - Vehicle + Saline
  - Vehicle + PTZ: P=0.0244
  - CBDV + Saline: P=0.0012
  - CBDV + PTZ

- **ARC** (synaptic plasticity)
  - Vehicle + Saline
  - Vehicle + PTZ: P=0.0374
  - CBDV + Saline: P=0.0221
  - CBDV + PTZ

- **CCL4** (neuronal inflammation)
  - Vehicle + Saline
  - Vehicle + PTZ: P=0.1720
  - CBDV + Saline: P=0.0323
  - CBDV + PTZ
The liquid formulation of pure plant-derived CBD (Epidiolex®) is being studied in clinical trials as a treatment for various orphan pediatric epilepsy syndromes.

The US FDA has granted Orphan Drug Designation in the treatment of Dravet and Lennox-Gastaut (LGS) syndromes:

- On March 2016 a first phase II n=120 20 mg/kg/d CBD clinical trial positive results in the treatment of seizures associated with Dravet syndrome were announced. A second study in this syndrome is recruiting now (aimed n=150)
- in June 2016 by positive results in the first LGS randomized placebo-controlled pivotal Phase III trial (n=171, 20mg/kg/d CBD dose vs. placebo)
- This September by the positive results of the second LGS randomized, double-blind, placebo-controlled Phase 3 (n=225) clinical trial, where CBD at 20 or 10 mg/kg/day doses achieved again a stat. significant median reduction in monthly seizures compared to placebo.
- GW has commenced a Phase III trial of CBD in Tuberous Sclerosis Complex seizures and expects to initiate a Phase III trial of CBD in infantile spasms in this fourth quarter of 2016.
CBD (Epidiolex®) Clinical Trials Program

**2015**
- Phase 3 (n=120) – positive*
- Phase 3 (n=150) recruiting
- Phase 3 (n=171) positive*
- Phase 3 (n=225) positive* 
  *P=0.01 for primary
  *P=0.01 for primary
  *P<0.005 for primary

**2016**
- Phase 3 (n=120) – positive*
- Phase 3 (n=150) recruiting
- Phase 3 (n=171) positive*
- Phase 3 (n=225) positive* 
  *P=0.01 for primary
  *P=0.01 for primary
  *P<0.005 for primary

**2017**
- Phase 3 (n=171) positive*
- Phase 3 (n=225) positive* 
  *P=0.01 for primary
  *P<0.005 for primary
- Phase 3 (n=~200) recruiting
- Two-part Phase 3

**Physician and State INDs (>900 patients)**
**Ongoing Treatment Data** - Other epilepsies

- Dravet Syndrome
- Lennox-Gastaut Syndrome
- Tuberous Sclerosis Complex
- Infantile Spasms
- Childhood Epilepsy Syndromes
Conclusions
What Do Modern Cannabis-Derived or Cannabinoid Products Require?:

Pharmaceutical production must-have:

- Quality accountable manufacturing
- Standardized by composition and dose
- Distribution and dispensation through monitored drug supply channels

Pre-clinical and Clinical Development plans have to be:

- Aimed to get for the patients in unmet need legitimate prescription administered drugs with proper health care insurance coverage
- Governed by the scientific method
- Follow the medicines agencies guidance, producing data from controlled clinical studies for regulatory bodies and physicians