New treatments for spasticity and other symptoms

Norbert Goebels, MD
Department of Neurology
Heinrich-Heine-University
Düsseldorf, Germany
Multiple Sclerosis Therapy

Causal Therapy

Immunmodulation -> Treatment of the underlying “autoimmune disease“:
-> Investment into the future

Symptomatic Therapy

Therapy of the symptoms of the disease:
-> “immediate (?) relief from symptoms“
Multiple Sclerosis: Scope of Symptoms

- **Optic Nerve**
  - Blurred vision
  - Reduced colour
  - Visual field deficit

- **Brainstem**
  - Articulation
  - Swallowing
  - Eye movements

- **Cerebrum**
  - Mentation
  - Concentration
  - Fatigue

- **Cerebellum**
  - Articulation
  - Coordination
  - Tremor, vertigo

- **Spinal cord**
  - Sensory symptoms
  - Spasticity
  - Palsy
  - Sphincter dysfunction
  - Sexual dysfunction

➢ And many others, often nonspecific symptoms!
## Ten most common MS Symptoms (UK survey)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Patients experiencing the symptom (%)</th>
<th>Patients rating the impact of the symptom as ‘moderate’ or ‘severe’ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>96</td>
<td>88</td>
</tr>
<tr>
<td>Balance and dizziness problems</td>
<td>92</td>
<td>74</td>
</tr>
<tr>
<td>Loss of mobility</td>
<td>91</td>
<td>79</td>
</tr>
<tr>
<td>Sensory problems</td>
<td>88</td>
<td>54</td>
</tr>
<tr>
<td>Bladder problems</td>
<td>87</td>
<td>70</td>
</tr>
<tr>
<td>Loss of memory and concentration</td>
<td>87</td>
<td>52</td>
</tr>
<tr>
<td><strong>Spasticity</strong></td>
<td><strong>82</strong></td>
<td><strong>54</strong></td>
</tr>
<tr>
<td>Vision problems</td>
<td>82</td>
<td>41</td>
</tr>
<tr>
<td>Pain</td>
<td>81</td>
<td>50</td>
</tr>
<tr>
<td>Bowel problems</td>
<td>74</td>
<td>45</td>
</tr>
</tbody>
</table>

\(^n = 2265.\) Adapted from [8].
Fampridine
Fig. 1  Effect of 4AP on compound action potential in rat dorsal root, showing myelinated (a) and unmyelinated (b) fibre components separately. Each trace is the mean of eight, obtained with a digital signal averager. Solid lines, control; dashed lines, following application of 4 mM 4AP.
Figure 1. Downstream effects of sustained-release (SR) fampridine. A: In multiple sclerosis, demyelination of axons exposes voltage-gated potassium channels, diminishing formation of a normal action potential and limiting neuronal conduction. B: With fampridine-SR, exposed voltage-gated potassium channels are blocked, restoring neuronal conduction and action potential formation.

Figure 2. Mechanism of action of sustained-release (SR) fampridine.
Fig 5. Reversible improvement from left internuclear ophthalmoplegia in the patient shown in Figure 4. (A) Before 4-aminopyridine (4-AP); (B) 75 minutes after 20 mg 4-AP; (C) reversal 220 minutes after 20 mg 4-AP. (Videotaped material.)
P-Kinetics of unsustained Formulation

Fig 2. Reversible improvement in critical flicker-fusion frequency after administration of 4-aminopyridine (4-AP) in a patient with multiple sclerosis with right optic nerve involvement (see text).
P-Kinetics of unsustained Formulation

Fig 2. Serial levels of 3,4-diaminopyridine (DAP) in Patient 1, with increasing doses demonstrating consistency in pharmacokinetics at different doses in a single patient.
Dalfampridine (Biogen-Idec / Acorda)

- 4-aminopyridine, sustained release (SR)
- Modifies axonal function
  -> Duration of action potential increases
- 10 mg Dalfampridine 2x/d (N=119) vs. Placebo (N=120)
- Timed 25 ft walk test

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Dalfampridine-SR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase</td>
<td>Phase III</td>
</tr>
<tr>
<td>Indication</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>Pharmacology description</td>
<td>Potassium channel antagonist</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Alimentary, by mouth</td>
</tr>
<tr>
<td></td>
<td>Alimentary, general</td>
</tr>
<tr>
<td>Chemical structure</td>
<td><img src="image" alt="Chemical structure" /></td>
</tr>
<tr>
<td>Pivotal trial(s)</td>
<td>1) MS-F202 study</td>
</tr>
<tr>
<td></td>
<td>2) Study MS-F203</td>
</tr>
<tr>
<td></td>
<td>3) Study MS-F204</td>
</tr>
</tbody>
</table>
Phase III Trial: Extended Release Oral Dalfampridine in Multiple Sclerosis (MSF204)

FIGURE 1: Diagram of the study schedule and design, with study visits shown by circled numbers. b.i.d. = twice daily.

Andrew D. Goodman, MD et al, Annals of Neurology 2010
Dalfampridine

Figure 1. MS-F203 trial design and primary end point–response criterion. (MS-F204 utilized a shortened 9 week stable dose phase, without an alteration in the number of visits.)
Primary Outcome: Percentage of Timed-Walk Responders (Pooled)

- Across trials, approximately 38% of patients treated with PR-fampridine showed a consistent increase in walking speed (timed-walk responders)

MS-F203 and 204 pooled

$P < 0.0001$

Timed-Walk Responders (%)

<table>
<thead>
<tr>
<th>Placebo (n=190)</th>
<th>PR-Fampridine (n=343)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.9%</td>
<td>37.6%</td>
</tr>
</tbody>
</table>

PR-Fampridine Shows Consistent Effects Regardless of MS Type

Treatment Group by Disease Type

PRMS=progressive-relapsing MS.

## Phase 3 Studies: Most Frequent Adverse Events (AEs)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo (n=191)</th>
<th>PR-Fampridine (n=348)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract infection</td>
<td>10.5%</td>
<td>14.9%</td>
</tr>
<tr>
<td>Falls</td>
<td>16.2%</td>
<td>14.4%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>2.6%</td>
<td>8.9%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2.6%</td>
<td>8.3%</td>
</tr>
<tr>
<td>Headache</td>
<td>2.6%</td>
<td>6.9%</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.1%</td>
<td>6.9%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>4.7%</td>
<td>6.6%</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>7.9%</td>
<td>6.0%</td>
</tr>
<tr>
<td>Back pain</td>
<td>1.6%</td>
<td>5.7%</td>
</tr>
<tr>
<td>Balance disorder</td>
<td>2.1%</td>
<td>5.7%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3.1%</td>
<td>5.2%</td>
</tr>
</tbody>
</table>

Studies MS-F203 and MS-F204: all AEs seen in >5% of PR-fampridine–treated patients.

Quantitative Benefit-risk Profile for PR-Fampridine

**Benefits**
- T25FW responders
- Improvement in MSWS-12 overall score
- Improvement in LEMMT
- Improvement in Ashworth score (spasticity)
- ≥20% Improvement in T25 walking speed
- CGI Score ≤3 at end DB period
- Average SGI score over DB period ≥6

**Risks**
- CNS excitation
- Urinary tract infection
- Seizures

**Derived Endpoints**
- Risk Difference and 95% CI (of 1000 Patients)

**Primary Endpoint**
- Favoring Placebo
- Favoring PR-Fampridine 10 mg

DB=double-blind; CNS=central nervous system.
Biogen Idec, data on file.
Retail-Price Dalfampridine (AMPYRA®) in the USA:

12.672,- USD / year (= 7,2 g)

7,2 g 4-Aminopyridin: 22,83 € (30,50 $)

-> 41.500 %
## Ten most common MS Symptoms (UK survey)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Patients experiencing the symptom (%)</th>
<th>Patients rating the impact of the symptom as ‘moderate’ or ‘severe’ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>96</td>
<td>88</td>
</tr>
<tr>
<td>Balance and dizziness problems</td>
<td>92</td>
<td>74</td>
</tr>
<tr>
<td>Loss of mobility</td>
<td>91</td>
<td>79</td>
</tr>
<tr>
<td>Sensory problems</td>
<td>88</td>
<td>54</td>
</tr>
<tr>
<td>Bladder problems</td>
<td>87</td>
<td>70</td>
</tr>
<tr>
<td>Loss of memory and concentration</td>
<td>87</td>
<td>52</td>
</tr>
<tr>
<td><strong>Spasticity</strong></td>
<td><strong>82</strong></td>
<td><strong>54</strong></td>
</tr>
<tr>
<td>Vision problems</td>
<td>82</td>
<td>41</td>
</tr>
<tr>
<td>Pain</td>
<td>81</td>
<td>50</td>
</tr>
<tr>
<td>Bowel problems</td>
<td>74</td>
<td>45</td>
</tr>
</tbody>
</table>

\(^n = 2265.\) Adapted from [8].
The stretch-reflex arc in MS spasticity

EUSPASM: “disordered sensorimotor control resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscles.”
Stevenson VL. Clin Rehab 2010

Patient description: “an unusual tightening of muscles that feels like leg stiffness, jumping of legs, a repetitive bouncing of the foot, muscle cramping in the legs or arms, legs going out tight and straight or drawing up.”
Rizzo et al. Mult Scler 2004
MS spasticity: causes

- Result of myelin and nerve fibre degradation
- MS plaques inhibit supraspinal control of reflex activity
- Impairment of functional movements of muscles of the extremities and of the trunk.
- Progressive damage -> loss of inhibition and a disruption of the stretch-reflex arc
MS spasticity severity
(% from US survey of > 20000 patients)

MS spasticity: symptom rating scales

The most frequently used have been:

- Ashworth Scale/Ashworth (modified) Scale
  - Numerical Rating Scale (NRS)
- Multiple Sclerosis Spasticity Scale (MSSS)
  - Daily mean spasm score
- Tardieu Scale (rarely used today)
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.
- 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.
Management of spasticity in MS patients

- 31% Other therapy
- 38% Pharmacological therapy
- 13% Pharmacological + other therapy
- 18% Untreated

Haas 2011
Symptomatic Therapy for Spasticity (1)

Treatment of contributing factors

- Fever
  - (Urinary tract) Infections
  - (Infected) decubitus ulcer
- Beta-Interferon associated increase of spasticity
Symptomatic Therapy for Spasticity (2)

Physiotherapy
- Multimodal rehabilitation including intense physiotherapy to reduce the extent of motor deficits
- Passive movement of major joints (motor-driven bicycle)
- If possible: Aerobic Fitness training
- Important: Sufficient Intensity and frequency

Medication:

<table>
<thead>
<tr>
<th>Substance (Drugname)</th>
<th>Dosage</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baclofen (e.g. Lioresal)</td>
<td>5-120 mg/d</td>
<td>Fatigue, nausea, confusion, ataxia</td>
</tr>
<tr>
<td>Tizanidin (e.g. Sirdalud)</td>
<td>2-24 mg/d</td>
<td>Hypotonia, dry mouth, nausea</td>
</tr>
<tr>
<td>Gabapentin (e.g. Neurontin)</td>
<td>300 – 2400 (3600) mg/d</td>
<td>Vertigo, fatigue, weakness</td>
</tr>
</tbody>
</table>
Symptomatic Therapy for Spasticity (3)

- Oral anti-spasticity agents (z.B. Baclofen/Lioresal®, Tizanidin/Sirdalud®)
  - cave: weakness
  - Increase dosage slowly (start with e.g. 3x2.5 mg Lioresal, 3x1 mg Sirdalud), -> maximum dosage according to effect, combine if necessary
- Botulinumtoxin A (z.B. Botox®)
- Intrathecal Baclofen (“Lioresal pump“)
- Intrathecal Triamcinolone (Volon A)
- Cannabis
Medical use of cannabis

- Cannabis has a long-history of use as both a medicine and as a recreational drug.
- Medically, street cannabis has been used to utilise its antispastic, muscle relaxant and pain relief effects.
- In a UK survey of persons using cannabis medically (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.

Street cannabis: concerns/limitations

- Legal issues.
- Street cannabis lacks standardization and purity
- In recent herbal samples high levels of Tetrahydrocannabinol (THC, psychoactive cannabinoid) and low levels of Canabidiol 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.
The endocannabinoid system

• 1990 breakthrough in the field of cannabinoid research: CB$_1$ receptor was discovered by Matsuda et al.
• 1992 Discovery of anandamide (endocannabinoid) by Devane et al.
• 1993 Discovery of CB$_2$ receptor by Munro et al.
• During the last 10 years the antispastic and analgesic effects of cannabinoids were investigated

New target for the regulation of physiological functions

Experimental studies showed, that the endocannabinoid system significantly changes in processes of spasticity.
The protein sequences of CB1 and CB2 receptors

**CB1 receptors:** hippocampus, basal ganglia, cortex, cerebellum, hypothalamus, pituitary, limbic structure and gastrointestinal tract.

**CB2 receptors:** immune cells and tissues and bone.
Endocannabinoids act as retrograde neuromodulators

CB: Cannabinoid; EC: Endocannabinoid; NT: Neurotransmitter

DiMarzo 2011
Cannabinoids: mechanism of action

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 CB₁ 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.

CNS forum. Cannabinoid receptors 2009.
Biozzi mice with chronic relapsing EAE CB1 agonists ameliorate spasticity

*Collin et al. 2007* p < 0.001 compared with baseline

---

* p < 0.001 compared with baseline
Rationale for the development of the standardised fix combination THC/CBD

• 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.
Standardized fix combination of THC/CBD

- Oromucosal spray contains two cannabinoids, which act synergistically:
  
  1) Tetrahydrocanabinol (THC)
  
  2) Canabidiol (CBD)

- THC is a CB₁- and CB₂-receptor agonist

- CBD is a CB₁- receptor antagonist and prevent the psychoactive effects of THC
THC and CBD: synergy (complementary effects)

Standardised fix combination THC/CBD: Composition and production

- First-in-class endocannabinoid system modulator comprising THC + CBD.
- Cannabinoid-based medicine derived from *Cannabis sativa*.
- Prepared from 2 cloned chemovars of *C. sativa* to ensure standardisation and quality.
- 10ml amber vials with a pump for oromucosal application.
Standardised fix combination THC/CBD manufacturing: sophisticated cultivation
Maximum plasma THC levels with the standardised fix combination THC/CBD and Street Cannabis (smoked)

## Clinical Overview (Phase III)

<table>
<thead>
<tr>
<th>Author/publ. year</th>
<th>Patients n =</th>
<th>Type of study</th>
<th>Primary endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wade 2004</td>
<td>160 / 3 centers</td>
<td>Pilot study</td>
<td>Score of five MS-symptoms: spasticity, spasms, bladder, tremor, pain (VAS)</td>
<td>1. endpoint: not sign.; 2. endpoint: spasticity alone: significant change</td>
</tr>
<tr>
<td>Collin 2007</td>
<td>189 / 12 centers</td>
<td>Pivotal study I</td>
<td>Change of spasticity (NRS)</td>
<td>Improvement statistically significant</td>
</tr>
<tr>
<td>Collin 2010</td>
<td>337</td>
<td>Pivotal study II</td>
<td>Change of spasticity (NRS)</td>
<td>PP: statistically significant</td>
</tr>
<tr>
<td>Novotna 2011</td>
<td>572 (Phase A) 241 (Phase B)</td>
<td>Pivotal study III</td>
<td>Change of spasticity (NRS)</td>
<td>Improvement statistically significant</td>
</tr>
<tr>
<td>Notcutt 2009</td>
<td>36</td>
<td>Tolerability</td>
<td>Time to failure of efficacy</td>
<td>Significance in favour of THC/CBD</td>
</tr>
<tr>
<td>Constantinescu 2006</td>
<td>444</td>
<td>Longterm safety study</td>
<td>Incidence of AEs and SAEs</td>
<td>Incidence comparable to short term studies</td>
</tr>
<tr>
<td>Wade 2006</td>
<td>137</td>
<td>Longterm safety study</td>
<td>Severity of worst symptoms (VAS)</td>
<td>Dosage &amp; severity constant -&gt; longterm efficacy</td>
</tr>
</tbody>
</table>
# Standardized fix combination THC/CBD: third pivotal clinical trial

<table>
<thead>
<tr>
<th>Status</th>
<th>Published (abstract available and full text pending)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>EU (multicentre)</td>
</tr>
<tr>
<td>Design</td>
<td>A 2-phase study: Phase A- single-blind response assessment and Phase B- a randomised, placebo-controlled, double-blind, parallel group study</td>
</tr>
<tr>
<td>Objective</td>
<td>To assess the efficacy and safety of the standardised fix combination THC/CBD vs. placebo in patients with MS spasticity</td>
</tr>
</tbody>
</table>
| Participants and schedule | • N = 572 MS adult patients  
• MS with spasticity and an inadequate response to drug therapy  
• Single-blind the standardised fix combination THC/CBD for 4 week, with initial responders (improving 20% or more from baseline NRS score) randomised to the standardised fix combination THC/CBD or placebo for 12 more weeks  
• 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  
• Modified Ashworth scale of spasticity  
• Timed 10-metre walk and motricity index  
• Spasm frequency and sleep disruption  
• Barthel ADL index  
• Carer’s global impression of change (CGIC)  
• Quality of Life |

Novotna et al. Eur J of Neurology 2011
Standardised fix combination THC/CBD*: third pivotal clinical trial: two-phase study design

Phase A (n=572)
- 7 day baseline period
- 4 weeks single blind THC/CBD*

Phase B (n=241)
- 12 weeks THC/CBD*
- 12 weeks Placebo
- Double blind randomised period

End of treatment/withdrawal

Visit 1  Visit 2  Visit 3
Visit 4 and 5
Visit 6

Novotna et al. Eur J of Neurology 2011
Standardized fix combination THC/CBD*: third pivotal clinical trial results: NRS resolution from phase A responders

![Graph showing NRS spasticity score over weeks for Sativex* and Placebo groups.](image-url)
Standardised fix combination THC/CBD third pivotal clinical trial: Well-being and quality of life (QoL)

- 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%).
Standardised fix combination THC/CBD: 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.
- The standardised fix combination THC/CBD does not exhibit the side effects typically associated with recreational cannabis use.

Standardised fix combination THC/CBD: AEs listed in the SmPC

<table>
<thead>
<tr>
<th>MeDRa System Organ Class disorders</th>
<th>Very common $\geq 1/10$</th>
<th>Common $\geq 1/100$ to $&lt;1/10$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition</td>
<td></td>
<td>Anorexia (including ↓appetite), ↑appetite</td>
</tr>
<tr>
<td>Psychiatric</td>
<td></td>
<td>Depression, disorientation, dissociation, euphoria</td>
</tr>
<tr>
<td>Nervous system</td>
<td>Dizziness</td>
<td>Amnesia, balance disorder, attention problems, memory impairment, somnolence, dysarthria, dysgeusia, lethargy</td>
</tr>
<tr>
<td>Eye</td>
<td></td>
<td>Blurred vision</td>
</tr>
<tr>
<td>Ear and labyrinth</td>
<td></td>
<td>Vertigo</td>
</tr>
<tr>
<td>Cardiac</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic, mediastinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td>Constipation, diarrhoea, nausea, dry mouth, glossodynia, vomiting, mouth ulcers, oral discomfort/pain,</td>
</tr>
<tr>
<td>General disorders and admin site</td>
<td>Fatigue</td>
<td>Application site pain, asthenia, feeling abnormal/drank, malaise</td>
</tr>
<tr>
<td>Injury. Poisoning and procedural</td>
<td></td>
<td>fall</td>
</tr>
</tbody>
</table>
## Treatment-related neurological AEs

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Standardised fix combination THC/CBD (n = 921)</th>
<th>Placebo (n = 853)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disturbance in attention</td>
<td>37 (4%)</td>
<td>2 (0.2%)</td>
</tr>
<tr>
<td>Memory impairment</td>
<td>14 (1.5%)</td>
<td>4 (0.5%)</td>
</tr>
<tr>
<td>Amnesia</td>
<td>9 (1%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Coordination abnormal</td>
<td>5 (0.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Cognitive disorder</td>
<td>2 (0.2%)</td>
<td>0</td>
</tr>
<tr>
<td>Depressed consciousness</td>
<td>2 (0.2%)</td>
<td>0</td>
</tr>
</tbody>
</table>

[From the standardised fix combination THC/CBD integrated safety analysis (Sept 1, 2007) from non-cancer studies.]

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.
Cognitive and Neuropsychiatric Effects

• Cognitive impairment occurs with the standardised fix combination THC/CBD, but in the majority of instances the symptoms were mild-to-moderate.

• Psychiatric AEs were also reported for the standardised fix combination THC/CBD, but they were mostly of mild-to-moderate severity.

• There is no evidence from RCTs that the standardised fix combination THC/CBD poses any long-term or irreversible neuropsychiatric or cognitive risk to patients.
Potential for abuse

- The standardised fix combination THC/CBD 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.

- No association 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.

- Lower abuse potential than equivalent doses of dronabinol, which itself is considered to have minimal abuse potential, in 23 abuse-prone recreational marijuana users.

Indication of standardized fix combination THC/CBD

**Add-on treatment**, for symptom improvement in patients with **moderate to severe spasticity** due to multiple sclerosis (MS), who have not responded adequately to other anti-spasticity medication
Standardised fix combination THC/CBD clinical efficacy: conclusions

- Results from well-controlled RCTs provide conclusive evidence of the efficacy of the standardised fix combination THC/CBD in MS-related spasticity.

- Randomized withdrawal of the standardised fix combination THC/CBD treatment provided definitive proof of long-term efficacy.

- The standardised fix combination THC/CBD not only reduced the symptoms associated with MS-spasticity, it also increased the ability of the patient to perform certain tasks and improved the perception of patients and their carers regarding functional status.
<table>
<thead>
<tr>
<th>Approved in:</th>
<th>Approval expected in:</th>
</tr>
</thead>
<tbody>
<tr>
<td>United Kingdom</td>
<td>Germany</td>
</tr>
<tr>
<td>Spain</td>
<td>Denmark</td>
</tr>
<tr>
<td>Czech republic</td>
<td>Sweden</td>
</tr>
<tr>
<td>Canada</td>
<td>Italy</td>
</tr>
<tr>
<td>New Zealand</td>
<td>Austria</td>
</tr>
</tbody>
</table>
Summary

• Standardised fix combination THC/CBD well tolerated
• Dizziness and fatigue are the most common AEs
• Most AEs are mild to moderate
• Only few withdrawals due to unwanted effects.
• Fix combination THC/CBD does not appear to pose risks of long-term or irreversible neuropsychiatric or cognitive impairment

• Famprine increases mobility in 1/3 of patients, currently not approved in EU, expensive